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(54) Title: SECRETED SOLUBLE $\alpha 2\delta$ -2, $\alpha 2\delta$ -3 OR $\alpha 2\delta$ -4 CALCIUM CHANNEL SUBUNIT POLYPEPTIDES AND SCREENING ASSAYS USING SAME

(57) Abstract: The present invention relates to secreted soluble $\alpha 2\delta$ -2, $\alpha 2\delta$ -3 or $\alpha 2\delta$ -4 calcium channel subunit polypeptides and their preparation, corresponding nucleic acids, recombinant vectors and host cells, as well as screening assays using same.

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Secreted soluble α 2 δ -2, α 2 δ -3 or α 2 δ -4 calcium channel subunit polypeptides
and screening assays using same

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FIELD OF THE INVENTION

The present invention relates to soluble α 2 δ -2, α 2 δ -3 or α 2 δ -4 calcium channel subunits and their preparation, corresponding nucleic acids, recombinant vectors and host cells comprising the same, as well as screening assays using same. The present invention relates to secreted soluble α 2 δ -2, α 2 δ -3 or α 2 δ -4 calcium channel subunit polypeptides and their preparation, corresponding nucleic acids, recombinant vectors and host cells, as well as screening assays using same

BACKGROUND OF THE INVENTION

15 Voltage-dependent Ca^{2+} channels (VDCCs) are heteromultimeric complexes present in both neuronal and non-neuronal tissues, including heart and skeletal muscle. VDCCs are minimally composed of three subunits: a pore-forming transmembrane α_1 subunit, a hydrophilic intracellular β subunit, and a membrane-associated $\alpha_2\delta$ subunit; a transmembrane γ subunit is also found in skeletal muscle tissue. Multiple subtypes and/or 20 splice variants of the α_1 , β , and $\alpha_2\delta$ subunits have been found.

25 Gabapentin ((1-aminomethyl)cyclohexane acetic acid or Neurontin) is a structural analogue of GABA, which is mainly used as an adjunctive therapy for epilepsy. Recent research suggests that gabapentin may also have clinical utility for various indications including anxiety and pain. Although designed as a lipophilic GABA-mimetic, gabapentin does not have a high affinity for either GABA_A or GABA_B receptors, GABA uptake sites, or the GABA-degrading enzyme GABA-transaminase (EC 2.6.1.19).

30 A novel high affinity binding site for [³H]gabapentin in rat, mouse, and porcine brains has been characterized. Recently, the [³H]gabapentin-binding protein was isolated from pig brain and identified as the $\alpha_2\delta$ -1 subunit of VDCCs. None of the prototypic anticonvulsant drugs displace [³H]gabapentin binding from the $\alpha_2\delta$ -1 subunit. [³H]Gabapentin-binding is stereospecifically inhibited by two enantiomers of 3-isobutyl GABA. The rank order of potency of gabapentin, and S- and R-isobutyl GABA, at the 35 [³H]gabapentin binding site mirrors their anticonvulsant activity in mice. However, electrophysiological studies have yielded conflicting data on the action of gabapentin at VDCCs.

The $\alpha_2\delta$ subunit is derived from a single gene, the product of which is extensively post-translationally modified particularly through the cleavage of the signal sequence. The polypeptide is cleaved to form disulfide-bridged α_2 and δ peptides, both of which are heavily glycosylated. Although it seems clear today that the α_2 and δ peptides are membrane-associated peptides, it is unclear whether these peptides comprise one or several transmembrane domains. Furthermore, the location, size and structural configuration of these eventual transmembrane domains remains to be determined.

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10 But in any event, the fact that $\alpha_2\delta$ is a membrane-associated protein, regardless of its precise structural configuration, renders its large scale expression in recombinant systems difficult. Indeed, as the $\alpha_2\delta$ protein is targeted to the membrane, it requires detergent solubilisation to release it for purification. This important drawback imposes considerable restrictions for any potential applications requiring large amounts of 15 recombinant protein. Furthermore, the various subtypes of $\alpha_2\delta$ subunits are different proteins with very low homologies. It is therefore extremely difficult to predict their respective behaviors, for example in gene truncation experiments.

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25 The only assay currently available for the screening of ligands that bind the $\alpha_2\delta$ subunit involves the use of pig membrane extracts as a source of the $\alpha_2\delta$ subunit. Such an assay presents major inconveniences. Firstly, because the assay material is a membrane extract, it is very difficult to accurately determine the protein composition from one assay preparation to another particularly with regard to the subtype. Also, the presence of various impurities in the assay preparation is a problem in small plate assays. Furthermore, as the protein preparation lacks homogeneity, the interaction between the targeted protein and the assay plate is often quite uneven. This renders the streamlining of the assay in a high throughput format almost impossible to achieve.

SUMMARY OF THE INVENTION

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The invention relates to forms of calcium channel $\alpha_2\delta$ subunits that are soluble and retain the functional characteristics of the full-length or wild-type $\alpha_2\delta$ subunit from which they derive.

In particular, the invention relates to forms of calcium channel $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 35 subunits that are soluble and retain the functional characteristics of the full-length or wild-type $\alpha_2\delta$ subunit from which they derive.

In the context of the present invention, a calcium channel $\alpha_2\delta$ subunit, in particular a calcium channel $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 sub-unit, is preferably a mammalian calcium channel $\alpha_2\delta$ subunit, in particular human or porcine.

In the context of the present invention, a calcium channel is preferably of cerebral

5 cortical origin and/or voltage-dependent.

In the context of the present invention, the inventors have found that it was possible to delete a portion of the nucleotide sequence encoding a eukaryotic, preferably a mammal cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$ subunit to yield a soluble secreted protein which retains its affinity for [³H]gabapentin.

10 Preferably, a "soluble form" means a form that is not membrane-associated. In particular, a "soluble form" means a form lacking membrane anchorage, a purified form, an isolated form, a free form and/or a secreted form.

Preferably, the "functional characteristics of the full-length or wild-type $\alpha_2\delta$ subunit" are the affinity for, the binding of or the interaction with ligands, especially [³H]gabapentin, 15 gabapentin and/or spermine.

The invention concerns:

1) A purified or isolated nucleic acid encoding a mammalian secreted soluble cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide.

20

2) A purified or isolated nucleic acid according to 1), comprising a polynucleotide having at least 90% identity with the sequence encoding :

- from amino-acid 1 to between amino-acids 1027 and 1062 of SEQ ID N°20 for $\alpha_2\delta$ -2,

25

- from amino-acid 1 to between amino-acids 984 and 1019 of SEQ ID N°22 for $\alpha_2\delta$ -3.

3) A purified or isolated nucleic acid according to 1), having at least 90% identity with the sequence encoding :

- from amino-acid 1 to between amino-acids 1047 and 1062 of SEQ ID N°20 for $\alpha_2\delta$ -2,

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- from amino-acid 1 to between amino-acids 1004 and 1019 of SEQ ID N°22 for $\alpha_2\delta$ -3.

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4) A purified or isolated nucleotide sequence according to 1) wherein said sequence is the sequence of SEQ ID N°1, SEQ ID N°2, SEQ ID N°3, SEQ ID N°7, SEQ ID N°8,

SEQ ID N°9, SEQ ID N°13, SEQ ID N°14, SEQ ID N°15, SEQ ID N°19 or SEQ ID N°21.

- 5) A purified or isolated nucleic acid, having at least 90% identity with the nucleotide sequence of SEQ ID N°19 or SEQ ID N°21.
- 6) A purified or isolated polynucleotide comprising at least 10 consecutive nucleotides of the nucleotide sequence of SEQ ID N°19 or SEQ ID N°21.
- 10 7) A polynucleotide probe or primer hybridizing, under stringent conditions, with the nucleotide sequence of SEQ ID N°19 or SEQ ID N°21.
- 8) A method for the amplification of a nucleic acid encoding a mammalian secreted soluble cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$ -n subunit polypeptide wherein n is 2, 3 or 4, said method comprising the steps of:
 - (a) contacting a test sample suspected of containing the target secreted soluble $\alpha_2\delta$ -n subunit nucleic acid, or a sequence complementary thereto, with an amplification reaction reagent comprising a pair of amplification primers located on either side of the $\alpha_2\delta$ -n subunit nucleic acid region to be amplified, and
 - 20 (b) optionally, detecting the amplification products.
- 9) A kit for the amplification of a nucleic acid encoding a secreted soluble $\alpha_2\delta$ -n subunit polypeptide wherein n is 2, 3 or 4, or a complementary sequence thereto in a test sample, wherein said kit comprises:
 - (a) a pair of oligonucleotide primers which can hybridize, under stringent conditions, to the secreted soluble $\alpha_2\delta$ -n subunit nucleic acid region to be amplified;
 - 25 (b) optionally, the reagents necessary for performing the amplification reaction.
- 30 10) A recombinant vector comprising a nucleic acid according to any one of 1) to 6).
- 11) A recombinant host cell comprising a nucleic acid according to any one of 1) to 6) or a vector according to 10).
- 35 12) A method for producing a secreted soluble $\alpha_2\delta$ -n subunit wherein n is 2, 3 or 4, and said method comprises the steps of:

(a) inserting the nucleic acid encoding the desired $\alpha_2\delta$ -n subunit polypeptide in an appropriate vector;

(b) culturing, in an appropriate culture medium, a host cell previously transformed or transfected with the recombinant vector of step (a);

5 (c) harvesting the culture medium thus obtained or lyse the host cell, for example by sonication or osmotic shock;

(d) separating or purifying, from said culture medium, or from the pellet of the resultant host cell lysate, the thus produced $\alpha_2\delta$ -n subunit polypeptide of interest.

10 13) A purified or isolated recombinant polypeptide comprising the amino acid sequence of a secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide.

14) A recombinant polypeptide according to 13), having at least 80% amino-acid identity with a polypeptide comprising :

15 - from amino acid 1 to between amino acids 1027 and 1062 of the amino acid sequence of SEQ ID N°20, or

- from amino acid 1 to between amino acids 1019 and 1079 of the amino acid sequence of SEQ ID N°22.

20 15) A recombinant polypeptide according to 14), wherein said recombinant polypeptide is selected from the group consisting of the amino acid sequences of SEQ ID n°4, SEQ ID n°5, SEQ ID n°6, SEQ ID n°10, SEQ ID n°11, SEQ ID n°12, SEQ ID n°16, SEQ ID n°17, SEQ ID n°18, SEQ ID n°23 and SEQ ID n°24.

25 16) A method for the screening of ligands which bind a cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$ -n subunit wherein n is 2, 3 or 4, said method comprising the steps of:

- contacting a secreted soluble recombinant calcium channel $\alpha_2\delta$ -n subunit polypeptide with:

30 - a ligand of interest; and

- a labelled compound which binds the $\alpha_2\delta$ -n subunit; and

- measuring the level of binding of the labelled compound to the $\alpha_2\delta$ -n subunit.

17) A method according to 16), wherein said method is a scintillation proximity assay.

35 18) A method according to 16), wherein said method is a flashplate assay.

19) A method according to 16), wherein said method is a filter binding assay.

20) A method according to 16), wherein said secreted soluble recombinant calcium channel $\alpha_2\delta$ -n subunit polypeptide is selected from polypeptides having at least 80%, 5 preferably 90%, more preferably 95%, and most preferably 98 or 99% amino-acid identity with the polypeptide comprising from amino acid 1 to between amino-acids 984 and 1063, preferably between amino-acids 994 and 1054, and most preferably between amino-acids 1019 and 1054 of SEQ ID N°5 or SEQ ID N°16.

10 21) A method according to 16), wherein said secreted soluble recombinant calcium channel $\alpha_2\delta$ -n subunit polypeptide is selected from the group consisting of SEQ ID N°4, 5, 6, 10, 11, 12, 16, 17 and 18,

15 22) A kit for the screening of ligands which bind a cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$ -n subunit wherein n is 2, 3 or 4, said kit comprising:

- a secreted soluble recombinant calcium channel $\alpha_2\delta$ -n subunit; and
- a labelled compound which binds to the $\alpha_2\delta$ -n subunit.

20 Hence, the invention concerns nucleotide sequence fragments of a cerebral cortical voltage dependent calcium channel $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit cDNA encoding a soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide (hereinafter a $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit). Preferably, these nucleotide sequences encode a soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide bearing a gabapentin or a [³H]gabapentin binding site. More preferably, the soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit nucleic acid is 25 derived from a eukaryotic, preferably a mammal, more preferably a human $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit.
bearing a gabapentin or a [³H]gabapentin binding site

A further object of the present invention concerns recombinant vectors comprising a 30 nucleic acid sequence encoding a soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide.

The invention also encompasses host cells and transgenic non-human mammals comprising said nucleic acid sequences or recombinant vectors.

35 The invention also concerns a soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide which is characterized in that it is a soluble secreted polypeptide having affinity for

[³H]gabapentin. Preferably, the soluble secreted polypeptide is derived from a mammal, more preferably a human $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit.

The inventors have also found that it was possible to use a soluble secreted form of a 5 voltage-dependant calcium channel $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide in an assay for the screening of ligands which bind the $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit.

The invention therefore also concerns a method for the screening of ligands which bind a calcium channel $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit.

10 The method comprises the steps of:

- contacting a secreted soluble recombinant calcium channel $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide with:
 - a ligand of interest; and
 - a labelled compound which binds a $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit; and
- measuring the level of binding of the labelled compound to the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit.

The invention also concerns a kit for the screening of ligands which bind a calcium channel $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit.

20 The kit comprises:

- a secreted soluble recombinant calcium channel $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide; and
- a labelled compound which binds a calcium channel $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit.

25

The invention also concerns :

- 1) A calcium channel $\alpha_2\delta$ subunit that is soluble and retain the functional characteristics of the full-length or wild-type $\alpha_2\delta$ subunit from which it derives.
- 30 2) A calcium channel $\alpha_2\delta$ subunit according to 1) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is of mammalian origin.
- 3) A calcium channel $\alpha_2\delta$ subunit according to 2) above wherein the mammalian origin is a human, a porcine, a rat or a mouse origin.
- 4) A calcium channel $\alpha_2\delta$ subunit according to 3) above wherein the mammalian 35 origin is a human origin.

- 5) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 4) above, wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is naturally expressed in the cerebral cortical.
- 6) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 5) above, wherein 5 the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is voltage-dependent.
- 7) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 6) above, wherein the $\alpha_2\delta$ subunit is cleaved.
- 8) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 7) above, wherein the $\alpha_2\delta$ subunit is cleaved into separate α_2 and δ peptides.
- 10 9) A calcium channel $\alpha_2\delta$ subunit according to 8) above, wherein the α_2 and δ peptides are disulfide-bridged.
- 10) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 6) above, wherein the $\alpha_2\delta$ subunit is not cleaved.
- 11) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 10) above 15 characterized in that it is purified or isolated.
- 12) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 11) above characterized in that it is processed as the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is naturally processed.
- 13) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 12) above 20 characterized in that it is producable by the baculovirus/insect cells expression system.
- 14) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 13) above characterized in that it is produced by the baculovirus/insect cells expression system.
- 15) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 14) above 25 characterized in that its δ peptide comprises at least the ligand-interacting part(s) of the complete δ peptide from which it originates
- 16) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 15) above characterized in that its δ peptide has a C-terminal truncation with respect to the complete δ peptide from which it originates, said truncation being sufficient to render the truncated δ peptide soluble.
- 30 17) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 16) above characterized in that its α_2 peptide comprises at least the ligand-interacting part(s) of the complete α_2 peptide from which it originates.
- 18) A calcium channel $\alpha_2\delta$ subunit according to any one of 15) or 17) above 35 characterized in that ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.
- 19) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 18) above characterized in that its α_2 peptide comprises at least the ligand-interacting part(s) of the

complete α_2 peptide from which it originates, its δ peptide comprises at least the ligand-interacting part(s) of the complete δ peptide from which it originates and its δ peptide does not comprise a part of the transmembrane domain of the complete δ peptide from which it originates which renders said calcium channel insoluble.

- 5 20) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 19) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates is $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4.
- 21) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°20.
- 10 22) A calcium channel $\alpha_2\delta$ subunit according to 20) or 21) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N°4, SEQ ID N° 5 or SEQ ID N° 6.
- 23) A calcium channel $\alpha_2\delta$ subunit according to any one of 20) to 22) above characterized in that the amino acid sequence of its unprocessed form comprises the region comprised between amino acid number 340 and amino acid number 1062 of SEQ ID N°20.
- 15 24) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°21.
- 20 25) A calcium channel $\alpha_2\delta$ subunit according to 20) or 24) characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 10, SEQ ID N° 11 or SEQ ID N° 12.
- 26) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 24) or 25) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 306 and amino acid number 1019 of SEQ ID N°20.
- 25 27) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°55.
- 30 28) A calcium channel $\alpha_2\delta$ subunit according to 20) or 27) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 53, SEQ ID N° 54 or SEQ ID N° 55.
- 29) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 27) or 28) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1050 of SEQ ID N°55.

30) A calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 20) above wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°33 or SEQ ID N°44.

31) A calcium channel $\alpha_2\delta$ subunit according to 20) or 30) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 34, SEQ ID N° 35, SEQ ID N° 36, SEQ ID N° 41, SEQ ID N° 42 or SEQ ID N° 43.

32) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 30) or 31) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1018 of SEQ ID N°33 or SEQ ID N°44.

33) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 30) or 31) above characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1018 of SEQ ID N°33 or SEQ ID N°44.

34) A calcium channel $\alpha_2\delta$ subunit according to any one of 20), 30), 31), 32) or 33) above characterized in that its α_2 peptide comprises the region comprised between amino acid number 302 and amino acid number 946 or 997 of SEQ ID N°33 or of SEQ ID N°44 and its δ peptide comprises the region comprised between amino acid number 984 and amino acid number 1018 of SEQ ID N°33 or of SEQ ID N°44.

35) A calcium channel $\alpha_2\delta$ subunit characterized in that its α_2 peptide and its δ peptide have 99%, 98%, 97%, 96%, or 95% homology or identity with the α_2 peptide and the δ peptide respectively of a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 34) above.

36) A nucleic acid molecule characterized in that its nucleotide sequence comprises a nucleotide sequence which encodes a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 35) above.

37) A nucleic acid molecule characterized in that its nucleotide sequence comprises a nucleotide sequence which encodes the α_2 peptide or the δ peptide of a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 35) above.

38) A nucleic acid molecule which hybridizes under stringent conditions with a nucleic acid molecule according to 36) or 37) above or 39) herebelow.

39) A nucleic acid molecule according to any one of 36) to 38) above which comprises SEQ ID N°1, SEQ ID N°2, SEQ ID N°3, SEQ ID N°7, SEQ ID N°8, SEQ ID N°9, SEQ ID N°13, SEQ ID N°14, SEQ ID N°15, SEQ ID N°30, SEQ ID N°31, SEQ ID N°32, SEQ ID N°38, SEQ ID N°39, SEQ ID N°40, SEQ ID N°50, SEQ ID N°51, or SEQ ID N°52.

- 40) A vector capable of expressing a nucleic acid molecule according to any one of 36) to 39) above.
- 41) An expression vector comprising a nucleic acid molecule according to any one of 36) to 39) above.
- 5 42) A vector according to 40) or 41) above which is a baculovirus vector.
- 43) A cell comprising a nucleic acid molecule according to any one of 36) to 39) above.
- 44) A cell comprising a vector according to 40), 41) or 42) above.
- 45) A cell according to 43) or 44) above which is a mammalian cell or an insect cell.
- 10 46) A composition comprising a calcium channel $\alpha_2\delta$ subunit according to any one of 7) to 9) above and a calcium channel $\alpha_2\delta$ subunit according to 10) above.
- 47) Screening assay using a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 35) above.
- 48) Screening assay according to 47) above which is an SPA assay, a Flashplate assay, a Nickel Flasplate assay, a Filter binding assay or a Wheat Germ Lectin flasplate assay.
- 15 49) Use of screening assay according to 47) or 48) above to detect or measure the binding or interaction of a ligand of a calcium channel $\alpha_2\delta$ subunit and a calcium channel $\alpha_2\delta$ subunit.
- 20 50) Use according to 49) above wherein the ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.
- 51) Kit to detect or measure the binding or interaction of a ligand of a calcium channel $\alpha_2\delta$ subunit and a calcium channel $\alpha_2\delta$ subunit comprising a calcium channel $\alpha_2\delta$ subunit according to any one of 1) to 35) above.
- 25 52) Kit according to 51) above wherein the ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.
- 53) Kit according to 51) or 52) above usable in an SPA assay, a Flashplate assay, a Nickel Flasplate assay, a Filter binding assay or a Wheat Germ Lectin flasplate assay.
- 30

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the dose response nature of [³H]gabapentin binding s- $\alpha_2\delta$ -2-6His and the maintenance of a constant low-level of non-specific binding (around 30-60cpm) independent of protein volume assayed.

Figure 2 illustrates the dose response nature of [³H]gabapentin binding s- $\alpha_2\delta$ -2-6His in the Nickel flashplate assay. As in the filter-binding assay, the level of non-specific binding is low (around 70-100cpm) and stable, independent of the volume of protein assayed or the point analysed on the time-course. A stable window is maintained for a period of at least 50 hours (between ~20 and 70 hours on the time-course)

Figure 3 illustrates the dose response nature of [³H]gabapentin binding s- $\alpha_2\delta$ -2-6His in the Wheat Germ lectin flashplate assay. Once again the level of non-specific binding is low (around 50-70cpm) and stable, independent of the volume of protein assayed or the point analysed on the time-course. The window is relatively stable over an extended period of time with just a gradual decline from the 15-hour time point (approximately 10% of the window every 24 hours).

DETAILED DESCRIPTION OF THE INVENTION

15 The invention concerns truncated $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit cDNA sequences. These truncated sequences encode soluble secreted polypeptides which retain their affinity for [³H]gabapentin.

20 Throughout the present specification, the expression "nucleotide sequence" is used to designate indifferently a polynucleotide or a nucleic acid. More precisely, the expression "nucleotide sequence" encompasses the nucleic material and the sequence information and is not restricted to the sequence information (i.e. the succession of letters chosen among the four base letters) that biochemically characterizes a specific DNA or RNA molecule.

25 As used interchangeably herein, the terms "oligonucleotides", "nucleic acids" and "polynucleotides" include RNA, DNA, or RNA/DNA hybrid sequences of more than one nucleotide in either single chain or duplex form.

30 Further to its general meaning understood by the one skilled in the art, the term "nucleotide" is also used herein to encompass modified nucleotides which comprise at least one of the following modifications (a) an alternative linking group, (b) an analogous form of purine, (c) an analogous form of pyrimidine, or (d) an analogous sugar. For examples of analogous linking groups, purines, pyrimidines, and sugars, see for example PCT publication N°WO 95/04064.

35 The polynucleotide sequences of the invention may be prepared by any known method, including synthetic, recombinant, or a combination thereof as well as through any purification methods known in the art.

A) Secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptides

The invention comprises polynucleotide sequences encoding a soluble secreted eukaryotic, preferably a soluble secreted mammal $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide. These sequences particularly include but are not restricted to 1) those 5 sequences encoding a soluble secreted polypeptide of this $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit which preferably retains its binding affinity for [³H]gabapentin and 2) nucleotide fragments useful as nucleic acid primers or probes for amplification or detection purposes.

The expression "soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit" is intended to designate 10 polypeptide sequences which, when produced by a recombinant host cell, are secreted at least partially into the culture medium rather than remaining associated with the host cell membrane.

1) cDNA fragments encoding soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3, $\alpha_2\delta$ -4 subunit 15 polypeptides

One of the important embodiments of the present invention concerns truncated nucleotide sequences of $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit cDNAs which encode soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptides. The inventors have found that it was possible to generate deletion mutants of $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit cDNAs which, 20 when expressed, produce a significant amount of soluble secreted proteins, preferably soluble secreted proteins, which retain their [³H]gabapentin binding affinity. These truncated nucleotide sequences of the invention are of significant value to the skilled person as they now allow fast and reliable access to significant concentrations of selected soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptides. To that end, the inventors 25 have determined the minimal and optimal fragment lengths required to express a polypeptide which: 1) binds [³H]gabapentin with sufficient affinity and; 2) is obtained in a soluble secreted form.

The discussion provided below provides comments on possible truncations, giving as an example the human $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit. However, given the very substantial 30 cross-species homology for $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit sequences, the comments below can also be applied to other eukaryotic species, and more particularly other mammalian species such as rat, mouse, rabbit or pig. Their $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit sequences, which for most are available in public databases, share a very substantial homology with the human $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit sequences.

35

The inventors believe that the soluble secreted $\alpha_2\delta$ -2 subunit polypeptides which are as close as possible to the native sequence and which are therefore more likely to retain

their native folding and hence their [³H]gabapentin binding properties are those corresponding to the native protein in which amino-acid stretch 1027 to the C-terminal end of the amino-acid sequence of SEQ ID N°20 has been deleted. The skilled scientist can quite easily determine within this amino-acid stretch the optimal $\alpha_2\delta$ -2 subunit 5 polypeptides.

The inventors also believe that the soluble secreted $\alpha_2\delta$ -3 subunit polypeptides which are as close as possible to the native sequence and which are therefore more likely to retain their native folding and hence their [³H]gabapentin binding properties are those 10 corresponding to the native protein in which amino-acid stretch 984 to C-terminal end of the amino-acid sequence of SEQ ID N°22 has been deleted. The skilled scientist can quite easily determine within this amino-acid stretch the optimal $\alpha_2\delta$ -3 subunit polypeptides.

15 The invention therefore particularly concerns a nucleotide sequence encoding a polypeptide having at least 80% identity with the polypeptide comprising from amino-acid 1 to between amino-acids 1027 and 1145, preferably to between amino-acids 1082 and 1145 of SEQ ID N°20.

Preferred nucleotide sequences include those of SEQ ID N°1, SEQ ID N° 2 and SEQ ID N°3.

20 The invention also concerns a nucleotide sequence encoding a polypeptide having at least 80% identity with the polypeptide comprising from amino-acid 1 to between amino-acids 984 and 1085, preferably to between amino-acids 1019 and 1085 of SEQ ID N°22.

25 Preferred nucleotide sequences include those of SEQ ID N°7, SEQ ID N° 8 and SEQ ID N°9.

30 The invention also encompasses isolated and/or purified nucleic acid molecules that hybridize under stringent conditions with the above nucleic acid sequences or a part thereof, and encode a soluble secreted $\alpha_2\delta$ subunit polypeptide having the ability to bind [³H]gabapentin.

B) Amplification of the soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit nucleotide sequences

35 Another object of the invention consists of a method for the amplification of a nucleic acid encoding a soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide, preferably a polypeptide bearing a [³H]gabapentin binding site, said method comprising the steps of:

5 (a) contacting a test sample suspected of containing the target $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit nucleic acid, a fragment or a variant thereof, or a sequence complementary thereto, with an amplification reaction reagent comprising a pair of amplification primers which can hybridize under stringent conditions, the $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit nucleic acid region to be amplified, and

(b) optionally, detecting the amplification products.

The expression [³H]gabapentin binding site, when used herein is intended to designate a site which can bind either [³H]gabapentin or other ligands such as (S+)-3-isobutyl gaba or (R-)-3-isobutyl gaba.

10 10 In a first preferred embodiment of the above method, the nucleic acid encodes a secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide of SEQ ID N°4, SEQ ID N°5, SEQ ID N°6, SEQ ID N°10, SEQ ID N°11, SEQ ID N°12, SEQ ID N°16, SEQ ID N°17 and SEQ ID N°18.

15 15 In a second preferred embodiment of the above amplification method, the amplification product is detected by hybridization with a labelled probe having a sequence which is complementary to the amplified region.

C) Recombinant vectors and hosts cells for the expression of a secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide

A most preferred system of expression of the calcium channel $\alpha_2\delta$ of the invention is the baculovirus/insect cell system. In fact, this system of expression allows to produce only the soluble form, is easy to use because the insect cells can be cultured without adherence and results in very high yield of production. Thus, this system allows mass-production of the calcium channel $\alpha_2\delta$ of the invention, provides an homogeneous production and is therefore particularly suitable for the preparation of this target for screening, in particular for high-throughput screening.

30 1) **Recombinant vectors**

The present invention also encompasses a family of recombinant vectors comprising any one of the nucleic acids described herein. Firstly, the invention deals with a recombinant vector comprising a nucleic acid selected from the group consisting of:

(a) a purified or isolated nucleic acid encoding a secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit having at least 80% amino acid identity with the polypeptide of SEQ ID N°20 or 22, or a sequence complementary thereto;

(b) a purified or isolated nucleic acid having at least 90% nucleotide identity with a polynucleotide selected from the group consisting of the nucleotide sequences of SEQ ID N°1, SEQ ID N°2, SEQ ID N°3, SEQ ID N°7, SEQ ID N°8, SEQ ID N°9, SEQ ID N°13, SEQ ID N°14, SEQ ID N°15 or a sequence complementary thereto;

5 (c) a purified or isolated polynucleotide comprising at least 10 consecutive nucleotides of a nucleic acid described in (a) or (b) or a sequence complementary thereto.

In a first preferred embodiment a recombinant vector of the invention is used to amplify the inserted polynucleotide of the invention in a suitable host cell, this polynucleotide being amplified every time the recombinant vector replicates.

10 Recombinant expression vectors comprising a nucleic acid encoding secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptides that are described in the present specification are also part of the invention. These include, but are not restricted to, nucleic acids encoding from amino-acid 1 to between amino-acids 1027 and 1145, preferably between amino-acids 1062 and 1145 of SEQ ID N°20, as well as nucleic acids encoding from amino-acid 1 to between amino-acids 984 and 1085, preferably between amino-acids 1019 and 1085, of SEQ ID N°22.

15 Another preferred embodiment of the recombinant vectors according to the invention consist of expression vectors comprising a nucleic acid encoding $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptides of the invention, and more preferably a nucleic acid encoding a polypeptide selected from the group consisting of the amino acid sequences of SEQ ID N°4, SEQ ID N°5, SEQ ID N°6, SEQ ID N°10, SEQ ID N°11, SEQ ID N°12, SEQ ID N°16, SEQ ID N°17 and SEQ ID N°18.

20 25 Within certain embodiments, expression vectors can be employed to express the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptides which can then be purified and for example, be used as an immunogen in order to raise specific antibodies directed against said secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptides.

30 35 Preferred eukaryotic vectors of the invention are listed hereafter as illustrative but not limitative examples: pcDNA3, pFLAG, pCMV-Script, pIND, pMC1NEO, pHIL, pGAPZA, pMT/V5-His-TOPO, pMT/V5-His, pAc5.1/V5-HisA, pDS47/V5-His, pcDNA4, pcDNA6, pEF1, pEF4, pEF6, pUB6, pZeoSV2, pRc/CMv2, pcDM8, pCR3.1, pDisplay, pSecTag2, pVP22, pEMZ, pCMV/Zeo, pSinRep5, pCEP, pREP, pHook-1

Preferred bacteriophage recombinant vectors of the invention are P1 bacteriophage vectors such as described by Sternberg N.L. (1992;1994).

A suitable vector for the expression of a soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide is a baculovirus vector that can be propagated in insect cells and in insect cell-lines. Specific suitable host vectors includes, but are not restricted to :pFastBac-1, 5 pIZ/V5-His, pBacMan-1, pBlueBac4.5, pBlueBacHis2, pMelBacA, pVL1392, pVL1393

The recombinant expression vectors from the invention may also be derived from an adenovirus such as those described by Feldman and Steig. (1996) or Ohno et al. (1994). Another preferred recombinant adenovirus according to this specific embodiment of the 10 present invention is the human adenovirus type two or five (Ad 2 or Ad 5) or an adenovirus of animal origin (French Patent Application n°FR 93 05 954).

a) Regulatory expression sequences

Expression requires that appropriate signals are provided in the vectors, said signals 15 including various regulatory elements such as enhancers/promoters from both viral and mammalian sources that drive expression of the genes of interest in host cells. The regulatory sequences of the expression vectors of the invention are operably linked to the nucleic acid encoding a soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide. As used herein, the term "operably linked" refers to a linkage of polynucleotide elements 20 in a functional relationship. For instance, a promoter or an enhancer is operably linked to a coding sequence if it affects the transcription of the coding sequence.

More precisely, two DNA molecules (such as a polynucleotide containing a promoter 25 region and a polynucleotide encoding a desired polypeptide or polynucleotide) are said to be "operably linked" if the nature of the linkage between the two polynucleotides does not : (1) result in the introduction of a frame-shift mutation or (2) interfere with the ability of the polynucleotide containing the promoter to direct the transcription of the coding polynucleotide.

Generally, recombinant expression vectors include origins of replication, selectable 30 markers permitting transformation of the host cell, and a promoter derived from a highly expressed gene to direct transcription of a downstream structural sequence. The heterologous structural sequence is assembled in an appropriate frame with the translation, initiation and termination sequences, and preferably a leader sequence capable of directing sequences of the translated protein into the periplasmic space or the extra-cellular medium.

35 In a specific embodiment wherein the vector is adapted for transfecting and expressing desired sequences in eukaryotic host cells, preferred vectors comprise an origin of replication from the desired host, a suitable promoter and an enhancer, and also any

necessary ribosome binding sites, polyadenylation site, transcriptional termination sequences, and optionally 5'-flanking non-transcribed sequences.

DNA sequences derived from the SV 40 viral genome, for example SV 40 origin early promoter, enhancer, and polyadenylation sites may be used to provide the required non-transcribed genetic elements.

b) Promoter sequences

Suitable promoter regions used in the expression vectors according to the invention are chosen taking into account the host cell in which the heterologous nucleic acids have to be expressed.

A suitable promoter may be heterologous with respect to the nucleic acid for which it controls the expression, or alternatively can be endogenous to the native polynucleotide containing the coding sequence to be expressed.

Additionally, the promoter is generally heterologous with respect to the recombinant vector sequences within which the construct promoter/coding sequence has been inserted.

Preferred eukaryotic promoters are the CMV, polyhidran or OPIE2.

2) Recombinant host cells

Host cells that have been transformed or transfected with one of the nucleic acids described herein, or with one of the recombinant vector, particularly recombinant expression vector, described herein are also part of the present invention.

Are included host cells that are transformed (prokaryotic cells) or are transfected (eukaryotic cells) with a recombinant vector such as one of those described above.

Preferred host cells used as recipients for the expression vectors of the invention are the following:

(a) prokaryotic host cells: *Escherichia coli*, strains. (i.e. DH10 Bac strain) *Bacillus subtilis*, *Salmonella typhimurium* and strains from species such as *Pseudomonas*, *Streptomyces* and *Staphylococcus*;

(b) eukaryotic host cells: HeLa cells (ATCC N°CCL2; N°CCL2.1; N°CCL2.2), Cv 1 cells (ATCC N°CCL70), COS cells (ATCC N°CRL 1650; N°CRL 1651), Sf-9 cells (ATCC N°CRL 1711), C127 cells (ATCC N°CRL-1804), 3T3 cells (ATCC N°CRL-6361), CHO cells (ATCC N°CCL-61), human kidney 293 cells (ATCC N° 45504; N°CRL-1573), BHK (ECACC N°84100 501; N°84111301), sf 9, sf 21 and hi-5 cells.

D) Production of recombinant secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptides

The present invention also concerns a method for producing one of the amino acid sequences described herein and especially a polypeptide selected from the group consisting of the aminoacid sequences of SEQ ID N°4, SEQ ID N°5, SEQ ID N°6, SEQ ID N°10, SEQ ID n°11, SEQ ID n°12, SEQ ID n°16, SEQ ID n°17 or SEQ ID n°18 wherein said method comprises the steps of:

- (a) inserting the nucleic acid encoding the desired amino acid sequence in an appropriate vector;
- (b) culturing, in an appropriate culture medium, a host cell previously transformed or transfected with the recombinant vector of step (a);
- (c) harvesting the culture medium thus obtained or lyse the host cell, for example by sonication or osmotic shock;
- (d) separating or purifying, from said culture medium, or from the pellet of the resultant host cell lysate, the thus produced recombinant polypeptide of interest.

In some instances, it is required to tag the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide prior to purification. The tag is then in most instances encoded into the nucleotide sequence that is needed to express the polypeptide. Examples of such tags include, but are not limited to sequences encoding C-myc, FLAG, a sequence of histidine residues, hemagglutin A, V5, Xpress or GST. Most of these tags can be incorporated directly into the sequence, for instance through PCR amplification by incorporating the appropriate coding sequence in one of the PCR amplification primers. However, the tag can also be introduced by other means such as covalent binding of the appropriate nucleic acid sequence encoding the tag moiety with the 3' or 5' end of the nucleic acid sequence encoding the polypeptide sequence. This is the case for GST.

Purification of the recombinant secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3, $\alpha_2\delta$ -4 subunit polypeptides according to the present invention is then carried out by passage onto a nickel or copper affinity chromatography column, such as a Ni NTA column or a Q-Sepharose column.

In another embodiment of the above method, the polypeptide thus produced is further characterized, for example by binding onto an immuno-affinity chromatography column on which polyclonal or monoclonal antibodies directed to the secreted soluble $\alpha_2\delta$ -2 subunit polypeptide of interest have been previously immobilised.

In another embodiment of the invention, the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3, $\alpha_2\delta$ -4 subunit polypeptide can be only partially purified. For instance, it can be purified along with other contaminating proteins using an appropriate chromatography matrix such as an ion-exchange chromatography column. In such instances, it is not required to tag the desired 5 polypeptide of interest.

The most preferred embodiment contemplated by the inventors concerns the use of a purified tagged secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide. A particularly preferred tag is a nucleotide sequence encoding from 2 to 10, and preferably 10 6 histidine residues. Examples of such tagged polypeptides are depicted on SEQ ID N°23 and 24.

With regard to the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide used subsequently in the screening assay of the invention, several possibilities are also open to 15 the skilled person.

In a first and preferred embodiment, the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide comprises a tag moiety which can be selected among the tags referred to above. Such tagged polypeptides are particularly useful in SPA or flashplate assays. A 20 preferred tag is the nucleotide sequence encoding histidine residues referred to above.

In a second embodiment, the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide can be used without a tag. This is the case for instance in SPA or flashplate assays comprising beads or plates coated with wheat germ lectin. In such an embodiment, the 25 tag is not needed as the carbohydrate moieties of the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide bind directly to the wheat germ lectin-coated beads or plates.

E) Purified recombinant secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 polypeptides

30 Another object of the present invention consists of a purified or isolated recombinant polypeptide comprising the amino acid sequence of a secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide.

Preferred isolated recombinant polypeptides of the invention include those having at least 35 80%, preferably 90%, more preferably 95, and most preferably 98 or 99%, amino-acid identity with polypeptides comprising from amino acid 1 to between amino-acids 1027 and 1145, preferably between amino-acids 1062 and 1145 of SEQ ID N°20, as well as

those having at least 80%, preferably 90%, more preferably 95, and most preferably 98 or 99%, amino-acid identity with polypeptides comprising from amino acid 1 to between amino-acids 984 and 1085, preferably between amino-acids 1019 and 1085 of SEQ ID N°22.

5

In a further preferred embodiment, the polypeptide comprises an amino acid sequence having at least 80%, preferably 90%, more preferably 95%, and most preferably 98% or 99% amino acid identity with the amino acid sequence of SEQ ID N°4, SEQ ID N°5, SEQ ID N°6, SEQ ID N°10, SEQ ID N°11, SEQ ID N°12, SEQ ID N°16, SEQ ID N°17 and SEQ ID N°18

10

More generally, the invention encompasses any secreted soluble $\alpha_2\delta$ subunit polypeptide encoded by a nucleic acid of the present invention.

F) Modified secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptides

15

The invention also relates to secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide comprising amino acid changes ranging from 1, 2, 3, 4, 5, 10, 20, 25, 30, 35, 40 substitutions, additions or deletions of one amino acid as regards to polypeptides of anyone of the amino acid sequences of the present invention. Preferred sequences are those of SEQ ID N°4, SEQ ID N°5, SEQ ID N°6, SEQ ID N°10, SEQ ID N°11, SEQ ID N°12, SEQ ID N°16, SEQ ID N°17 and SEQ ID N°18.

20

In the case of an amino acid substitution in the amino acid sequence of a polypeptide according to the invention, one or several consecutive or non-consecutive amino-acids are replaced by "equivalent" amino-acids. The expression "equivalent" amino acid is used herein to designate any amino acid that may be substituted for one of the amino-acids belonging to the native protein structure without decreasing the binding properties of the corresponding peptides to the antibodies raised against the polypeptides of the invention. In other words, the "equivalent" amino-acids are those which allow the generation or the synthesis of a polypeptide with a modified sequence when compared to the amino acid sequence of the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptides of interest, said modified polypeptide being able to bind to the antibodies raised against the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide of interest and/or to induce antibodies recognizing the parent polypeptide.

25

Alternatively, amino acid changes encompassed are those which will not abolish the biological activity of the resulting modified polypeptide. These equivalent amino-acids may be determined either by their structural homology with the initial amino-acids to be replaced, by the similarity of their net charge or of their hydrophobicity, and optionally

by the results of the cross-immunogenicity between the parent peptides and their modified counterparts.

The peptides containing one or several "equivalent" amino-acids must retain their specificity and affinity properties to the biological targets of the parent protein, as it can

5 be assessed by a ligand binding assay or an ELISA assay.

Examples of amino-acids belonging to specific classes include Acidic (Asp, Glu), Basic (Lys, Arg, His), Non-polar (Ala, Val, Leu, Ile, Pro, Met, Phe, Trp) or uncharged Polar (Gly, Ser, Thr, Lys, Tyr, Asn, Gln) amino-acids.

Preferably, a substitution of an amino acid in $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide

10 of the invention, or in a peptide fragment thereof, consists in the replacement of an amino acid of a particular class for another amino acid belonging to the same class.

By an equivalent amino acid according to the present invention is also contemplated the replacement of a residue in the L-form by a residue in the D form or the replacement of a Glutamic acid (E) residue by a Pyro-glutamic acid compound. The synthesis of peptides containing at least one residue in the D-form is, for example, described by Koch (1977).

15 A specific embodiment of a modified peptide of interest according to the present invention, includes, but is not limited to, a peptide molecule, which is resistant to proteolysis. This is a peptide in which the -CONH- peptide bond is modified and replaced by a (CH₂NH) reduced bond, a (NHCO) retro inverso bond, a (CH₂O) methylene-oxy bond, a (CH₂S) thiomethylene bond, a (CH₂CH₂) carba bond, a (CO-CH₂) cetomethylene bond, a (CHOH-CH₂) hydroxyethylene bond, a (N-N) bound, a E-alcene bond or also a -CH=CH-bond.

The invention also encompasses secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide in which at least one peptide bond has been modified as described above.

20 The polypeptides according to the invention may also be prepared by the conventional methods of chemical synthesis, either in a homogenous solution or in solid phase. As an illustrative embodiment of such chemical polypeptide synthesis techniques, it may be cited the homogenous solution technique described by Houbenweyl (1974).

25 The secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide of interest, or a fragment thereof may thus be prepared by chemical synthesis in liquid or solid phase by successive couplings of the different amino acid residues to be incorporated (from the N-terminal end to the C-terminal end in liquid phase, or from the C-terminal end to the N-terminal end in solid phase) wherein the N-terminal ends and the reactive side chains are previously blocked by conventional groups.

30 35 For solid phase synthesis, the technique described by Merrifield (1965a; 1965b) may be used in particular.

G) Antibody production

The secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptides of the invention and their peptide fragments of interest can be used for the preparation of antibodies.

5 Polyclonal antibodies may be prepared by immunization of a mammal, especially a mouse or a rabbit, with a polypeptide according to the invention that is combined with an adjuvant of immunity, and then by purifying the specific antibodies contained in the serum of the immunized animal on an affinity chromatography column on which has previously been immobilized the polypeptide that has been used as the antigen.

10 Monoclonal antibodies may be prepared from hybridomas according to the technique described by Kohler and Milstein (1975).

The present invention also deals with antibodies produced by the trioma technique and by the human B-cell hybridoma technique, such as described by Kozbor et al. (1983).

15 Antibodies of the invention also include chimeric single chain Fv antibody fragments (US Patent N° 4,946,778; Martineau et al., (1998), antibody fragments obtained through phage display libraries Ridder et al. (1995) and humanized antibodies (Leger et al., (1997)).

H) Screening assays

20 The invention concerns a method for the screening of ligands which bind soluble secreted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide. More particularly, the targeted $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit binding site is preferably the [3 H]gabapentin binding site. The various parameters of the method of the invention are described in further detail below.

25 **1) Labelled compounds which bind the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide**

In cases where the $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 binding site is the [3 H]gabapentin binding site, the preferred labelled compound which can be used is of course gabapentin itself. However, gabapentin is not the only labelled compound which can be used in this context. Indeed, it has been previously demonstrated that saturation binding analyses on porcine synaptic plasma cerebral cortex membranes performed in the presence of L-leucine indicate a competitive interaction of the amino acid with the [3 H]gabapentin binding site, significantly reducing [3 H]gabapentin binding affinity for the site. The inventors believe that this competitive interaction is true across all the amino-acids listed in table 1 below.

TABLE 1

Binding affinities of selected amino acids ($IC_{50} < 500\text{nM}$) for the [^3H]gabapentin site
in porcine cortical membranes

5

COMPOUND	IC_{50} (nM) ARITHMETIC MEAN (N=3) \pm S.E.M.
Gabapentin	42.1 ± 5.5
L-Norleucine	23.6 ± 6.7
L-Allo-Isoleucine	32.8 ± 6.0
10 L-Methionine	49.6 ± 10.0
L-Leucine	61.3 ± 20.9
L-Isoleucine	68.8 ± 1.9
L-Valine	330 ± 18
L-Phenylalanine	351 ± 89

15

It is therefore possible to use commercially available labelled forms of these high affinity ligands in replacement of gabapentin. The utility of [^3H]L-leucine has been demonstrated in a filter binding assay and in a flashplate assay format. The inventors believe that labelled amino acids but also other compounds, with affinities preferably below 500 nM in the binding assay can be used as replacements of gabapentin.

With regard to the label, several embodiments can be used in the context of the invention. Preferred labels are of course radioactive labels, a list of which is provided further in this specification.

25

2) Assay formats and conditions

Several assay formats can be used to carry out the method of the present invention. Preferred assay formats include scintillation assays such as the scintillation proximity assay (SPA) or the flashplate assay. Other assay formats well known to those skilled in the arts such as the filter binding assay and the centrifugation assay are also contemplated in the present invention.

SPA and flashplate assays are preferred assay formats for the present invention. Additional details on these assays are provided below.

35

Scintillation assay format

Scintillation assays technology either involves the use of scintillant beads (for the SPA assay) or plates (for the flashplate assay). SPA beads are usually made from either cerium-doped yttrium ion silicate (γ 2SiO5:Ce) or polyvinyltoluene (PVT) containing an organic scintillant such as PPO. Flashplates commonly used are those such as Ni chelate flashplates although other flashplates can also be used, such as the Wheat Germ lectin flashplate.

Assays are usually carried out in aqueous buffers using radioisotopes such as 3 H, 125 I, 14 C, 35 S or 33 P that emit low-energy radiation, the energy of which is easily dissipated in an aqueous environment. For example, the electrons emitted by 3 H have an average energy of only 6 keV and have a very short path length (-1 ~tm) in water. If a molecule labelled with one of these isotopes is bound to the bead or flashplate surface, either directly or via interaction with another molecule previously coupled to the bead or flashplate, the emitted radiation will activate the scintillant and produce light. The amount of light produced, which is proportional to the amount of labelled molecules bound to the beads, can be measured conveniently with a liquid scintillation (LS) counter. If the labelled molecule is not attached to the bead or a flashplate surface, its radiation energy is absorbed by the surrounding aqueous solvent before it reaches the bead, and no light is produced. Thus, bound ligands give a scintillation signal, but free ligands do not, and the need for a time-consuming separation step, characteristic of conventional radioligand binding assays, is eliminated. The manipulations required in the assays are reduced to a few simple pipetting steps leading to better precision and reproducibility.

The conditions under which SPA and flashplate assays are performed in the context of the present invention are provided below.

Scintillation assay conditions**a) SPA assay**

The SPA assays is first developed to optimize the conditions under which the radioligand binds the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide. The parameters which can be varied to optimize radioligand binding in a typical SPA assay using Amersham beads include assay temperature, $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide interaction with the radioligand and the SPA beads, radioligand concentration as well as pH variations.

The temperature at which the assay can be carried out can vary from 1 to 30°C. Preferred temperatures range from 18 to 23°C, with 21°C being the most preferred temperature. The interaction of the $\alpha_2\delta$ subunit polypeptide with the SPA beads can be optimized by adjusting the concentration of the polypeptide and by introducing a reagent 5 which will favor this interaction. When 50 mg of Amersham SPA beads are used, the $\alpha_2\delta$ -1 subunit polypeptide concentration may vary from 0.1 to 10 pmoles per well, with the optimal concentration being generally around 5 to 6 pmoles per well.

As for the reagent favoring the interaction between the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or 10 $\alpha_2\delta$ -4 subunit polypeptide and the radioligand as well as the Amersham SPA beads, the inventors found that imidazole could be efficiently used for that purpose when the $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide is tagged with an amino acid sequence including 6 histidine residues. Furthermore, and more importantly, it was found that imidazole also enhanced binding of the radioligand to the $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 polypeptide.

15 The concentration of the radioligand is evaluated with respect to the concentration of secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide present in the assay medium. Generally, the concentration of radioligand varies from 1 nM to 100 nM. A preferred 20 $[^3\text{H}]$ gabapentin concentration is about 5 to 20 nM, with a most preferred concentration being about 10 nM. A preferred $[^3\text{H}]$ leucine concentration is also about 5 to 20 nM, with a most preferred concentration being about 10 nM. It is to be noted that the concentration of other radioligands having affinities similar to those of $[^3\text{H}]$ gabapentin and $[^3\text{H}]$ leucine should also be in the range of about 5 to 20 nM.

25 Once the optimal radioligand binding conditions have been determined, a test ligand can be introduced in the assay medium to evaluate the level of displacement of the radioligand. The concentration of test ligand to be introduced in the assay medium usually varies from 0.1 nM to about 100 μM . A preferred test ligand concentration of about 10 μM is usually a starting point in a high throughput screening assay. Then, 30 depending on the number of hits obtained, it may be lowered or increased.

It is to be noted that the parameters set forth above, which have been evaluated for a typical SPA assay using Amersham SPA beads can be adjusted by the skilled person, for example if SPA beads of a different type are used.

35

b) Flashplate assay

Similarly to the SPA assays, the flashplate can first be developed in order to optimize the conditions under which the radioligand binds the $\alpha_2\delta$ subunit polypeptide. The parameters which can be varied to optimize radioligand binding in a typical flashplate assay using NEN Ni chelate flashplates or the Wheat Germ lectin flashplates also include 5 assay temperature, secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide interaction with both the radioligand and the flashplates, radioligand concentration as well as pH variations.

The temperature at which the assay can be carried out can vary from 1 to 30°C. 10 Preferred temperatures range from 18 to 23°C, with 21°C being the most preferred temperature.

The interaction of the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide with the flashplates can be optimized by adjusting the concentration of the polypeptide and by 15 introducing a reagent which will favor this interaction. When a standard NEN Ni chelate flashplate is used, the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide volume usually varies between 0.5 and 20 μ l for a concentration of secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide of 0.6 pmol/ μ l. As the published maximum binding 20 capacity of NEN p plates is about 6 pmol per well, the inventors consider that an optimal concentration of secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide is probably around 5 pmol per well at 8 μ l.

With regard to the reagent favoring the interaction between the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide and the radioligand as well as the flashplates, the 25 inventors believe that imidazole could also be efficiently used for that purpose when the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide is tagged with an amino acid sequence including 6 histidine residues. The inventors also believe that imidazole concentrations can substantially enhanced binding of the radioligand to the secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 polypeptide. The optimal concentration of imidazole used 30 to enhance radioligand binding varies depending on the concentration of secreted soluble $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide used in the assay. For instance, when the volume of the $\alpha_2\delta$ -1 subunit polypeptide is about 10 μ l ($\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 polypeptide concentration of 0.6 pmol/ μ l), the optimal imidazole concentration can vary 35 between 1 and 20 mM, with a concentration of about 10 mM being preferred. As mentioned previously, other compounds such as histidine as well as pH variations may be used to enhance radioligand binding.

The concentration of the radioligand is evaluated with respect to the concentration of $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4 subunit polypeptide present in the assay medium. Generally, the concentration of radioligand varies from 1 nM to 100 nM. A preferred [³H]gabapentin concentration is about 5 to 20 nM, with a most preferred concentration being about 10 nM. A preferred [³H]leucine concentration is also about 5 to 20 nM, with a most preferred concentration being about 10 nM. It is to be noted that the concentration of other radioligands having affinities similar to those of [³H]gabapentin and [³H]leucine should also be in the range of about 5 to 20 nM.

Once the optimal radioligand binding conditions have been determined, a test ligand can be introduced in the assay medium to evaluate the level of displacement of the radioligand. The concentration of test ligand to be introduced in the assay medium usually varies from 0.1 nM to about 100 μ M. A preferred test ligand concentration of about 10 μ M is usually a starting point in a high throughput screening assay. Then, depending on the number of hits obtained, it may be lowered or increased.

The inventors have tested the displacement of a particular radioligand, [³H]gabapentin, with (S+)-3-isobutyl gaba. The data provided in the examples which follow clearly shows that the assay can be used in high throughput competition studies.

The invention also resides in a product or ligand isolated, identified or selected using the above screening methods or kits, for use as a medicament or as a lead for further drug development purposes. As indicated above, the compounds are potentially useful for treating disorders of the nervous system, including epilepsy, pain and anxiety.

Further aspects and advantages of the present invention will be described in the following examples, which should be regarded as illustrative and not limiting the scope of the present application.

EXAMPLESExample 15 Construction of a nucleotide sequence encoding a soluble secreted human $\alpha_2\delta$ -2 subunit polypeptide deletion mutant of SEQ ID N°23a) Primer design

PCR primers were designed to generate the secreted soluble human $\alpha_2\delta$ -2 deletion 10 mutant of SEQ ID N° 23 as follows:

5' PCR primer: This was designed to engineer in a KOZAK translation initiation consensus sequence prior to the coding sequence (Kozak *JBC* 266 19867-19870)

3' PCR primer: This was designed to engineer in six histidine residues followed by a stop-codon at the desired location in the coding sequence. In addition to the stop codon 15 the $\alpha_2\delta$ -2 primers also included an *Eco* RI restriction site.

The bold region in each primer sequence denotes the 'tagged' region; addition of sequences not present in the template. Primers were custom synthesized by Perkin Elmer Applied Biosystems UK to the ABI ready pure grade, supplied lyophilized then 20 resuspended to 15 μ M in 10mM TE. JB197 and 198 were provided with 5' phosphate groups:

5' Primer JB197 (5' -**TCGCCACCATGGCGGTGCCGGCTC**-3' , SEQ ID N°25)

25 3' Primer JB198 (5' -
TCGGAATTCCCTCAGTGATGGTGATGGTGATGGGCCCGCGGCCACAGTC-3' , SEQ ID N°26)

b) Protocol for PCR mediated 5' Kozak and 3' 6His tagging of human $\alpha_2\delta$ -2

30 The full length human $\alpha_2\delta$ -2 gene (Gen Bank Accession Number AF042792) in a pcDNA 3 vector as described in Brown, J.P. and Gee, N.S., (Cloning and deletion mutagenesis of the $\alpha_2\delta$ calcium channel subunit from porcine cerebral cortex, *The journal of biological chemistry*, 273(39):25458-25465) was used as the template in the 35 following PCR reaction.

The reagents were added in the following order in triplicate to a 96 well PCR plate:

	<i>μl</i>
<i>10x Pfx Amplification buffer</i>	5
<i>10mM dNTPs</i>	1.5
<i>50mM MgSO₄</i>	1
5 <i>15μM JB197</i>	1.5
<i>15μM JB198</i>	1.5
<i>100ng/μl pcDNA3.1-humans-α₂δ-2</i>	1
<i>10x PCR Enhancer</i>	5
<i>H₂O</i>	32.7
10 <i>2.5 UNITS/μl PFX POLYMERASE</i>	<i>0.8μl</i>

The plate was then cycled on an MJ Tetrad DNA engine according to the following cycling conditions:

15 *94°C / 2mins*

followed by:

for 30 cycles *94°C / 45sec*
58°C / 45sec
68°C / 4mins

20 *followed by:*

68°C / 10mins

followed by:

hold at 4°C

25 The 3366bp product was then gel purified from a 1% TAE agarose gel using QIAEX beads and eluted in approximately 50μl TE.

Example 2

Cloning of the PCR fragments of Example 1 into the Baculovirus transfer vector

30 *pFastBac1*

The PCR products of Example 1 were cloned into *Stu* I digested, calf intestinal phosphatase dephosphorylated, phenol chloroform extracted and QIAEX gel purified pFastBac1 (Life Technologies) using the Rapid DNA ligation kit (Roche Diagnostics)

35 transforming XL1-blue (α₂δ-1b) *E. Coli* cells:

a) Screening for positive recombinants

Given that the PCR product was cloned by blunt-end ligation a screen was required to select a recombinant with the gene ligated in the positive orientation with respect to the polyhedrin promoter in pFastBac1. This was achieved by restriction digest of miniprep

5 DNA (Qiagen miniprep kit) prepared from colony minicultures and analysis on a 1% TAE agarose gel. A positive clone was identified according to the following digest patterns:

SEQ ID N° 23 in pFastBac1

10 *Eco* RI digest performed on miniprep DNA

	Predicted fragments (bp)
PCR product cloned in a positive orientation	4773 and 3368
PCR product cloned in a negative orientation	8127 and 14

15 **b) Sequencing analysis of selected clones**

One positive was selected for this clone and used to prepare a plasmid DNA stock of the desired construct (QIAGEN maxi kit). Confirmatory sequence reactions were performed using the Big Dye terminator sequencing kit and run on an ABI 310 Prism Genetic Analyzer. Sequence analysis of both coding strands was performed using a selection of sequencing oligonucleotide primers.

Example 3

Protocol for establishing baculovirus banks for the expression of the $\alpha_2\delta-2$ deletion mutant SEQ ID N°23

25

Essentially, the protocol used to generate the baculovirus banks is that outlined in the Life Technologies Bac-to-Bac™ baculovirus expression systems manual.

a) Transposition of DH10Bac *E. coli* cells

30 One ng (5 μ l) of the recombinant pFastBac-1 construct containing the nucleotide sequence encoding the porcine $\alpha_2\delta-2$ deletion mutant of SEQ ID N°23 was added to 100 μ l of DH10Bac cells thawed on ice. The cells were then mixed gently by tapping the tube then incubated on ice for 30 minutes before heat shock treatment by incubation in a 42°C water bath for 45 seconds. The mixture was then chilled on ice for 2 minutes before 35 the addition of 900 μ l of S.O.C. medium. The mixture was then placed in a shaking incubator (200rpm) at 37°C for 4 hours. The cells were then serially diluted (10 fold dilutions from 10⁻¹ to 10⁻³) and 10 μ l of each dilution plated on LB agar plates containing

50 μ g/ml kanamycin, 7 μ g/ml gentamicin, 10 μ g/ml tetracycline, 100 μ g/ml Bluo-gal and 40 μ g/ml IPTG. The plates were incubated at 37°C for between 1 and 3 days until discrete colonies of blue and white colour were discernible.

5 **b) Isolation of recombinant DNA**

White colonies (containing the recombinant bacmid) were picked and grown for 24 hours (to stationary phase) at 37°C with shaking (200rpm) in 2ml of LB containing 50 μ g/ml kanamycin, 7 μ g/ml gentamicin and 10 μ g/ml tetracycline. 1.5ml of culture was then transferred to a microfuge tube and centrifuged at 14,000xg for 1 minute. The supernatant 10 was removed and the cells resuspended gently in 0.3ml of 15mM Tris-HCl (pH8.0), 10mM EDTA, 100 μ g/ml RNase A. 0.3ml of 0.2N NaOH, 1% SDS was then added and the mixture mixed gently before incubation at 22°C for 5 minutes. Then 0.3ml of 3M Potassium acetate (pH5.5) was added and the sample placed on ice for 10 minutes. After 15 centrifugation at 14,000xg for 10 minutes the supernatant was transferred to a tube containing 0.8ml of isopropanol, mixed then placed on ice for 10 minutes before centrifugation at 14,000xg for 10 minutes. The supernatant was then discarded and the pellet rinsed with 0.5ml of 70% ethanol before centrifugation at 14,000xg for 5 minutes. This 70% ethanol rinse was then repeated before removing all of the supernatant and air 20 drying the pellet for 10 minutes at room temperature. The pellet was finally resuspended in 40 μ l of TE.

25 **c) Transfection of sf9 cells with the recombinant bacmid DNA**

A 6-well tissue culture plate was seeded with 0.9×10^6 sf9 cells (cells at log phase having grown from a culture passaged at 0.3×10^6 cells/ml) per 35mm well in 2ml of Sf-900 II SFM media containing 50units/ml penicillin and 50 μ g/ml streptomycin. Cells were left to attach at 27°C for 1 hour. Bacmid DNA prepared as described above (5 μ l) was added to 200 μ l of Sf-900 II SFM media containing 6 μ l of CELLFECTIN and mixed before 30 incubation at room temperature for 45 minutes. The cells were washed once with 2ml of Sf-900 II SFM media without antibiotics then 0.8ml of Sf-900 II SFM media was added to each tube containing the lipid-DNA complex. The wash buffer was removed from the cells and the 1ml of diluted lipid-DNA complex overlaid on the cells. The cells were incubated for 5 hours at 27°C after which time the transfection mixture was removed and 2ml of Sf-900 II SFM media containing 50units/ml penicillin and 50 μ g/ml streptomycin was added. The cells were then incubated for 72 hours.

35

After incubation for 72 hours the media was removed from the cells and centrifuged at 500xg for 5 minutes. The supernatant was then transferred to a fresh tube, this was

labelled as the P0 bank and stored at 4°C in the dark. The P1 bank was prepared by passaging sf9 cells at approx 5×10^6 cells/ml to 2×10^6 cells/ml (100ml in a 250ml Erlenmeyer flask) and adding 0.5ml of the P0 bank harvested above. The cells were then incubated shaking (200rpm) at 27°C for 4 days. Under sterile conditions the culture was 5 centrifuged at 500xg for 10 minutes and the supernatant 0.2µM filtered (P1 bank). The P2 bank was prepared by adding 2ml of P1 bank per 400ml culture (in 1L Erlenmeyer flasks) passaged as above to 2×10^6 cells/ml. The culture was incubated as before for 4 days and the supernatant harvested and filtered as described for the P1 bank. The supernatant was first pooled then aliquoted (10ml) and stored at 4°C.

10

Example 4**Expression of the $\alpha_2\delta$ -2 deletion mutant of SEQ ID N°23**

To sf9 cells passaged from $\sim 5 \times 10^6$ cells/ml to 2×10^6 cells/ml in Sf-900 II SFM media was added 0.1ml virus per 100ml of cells of the appropriate viral bank (400ml volumes 15 in 1L Erlenmeyer flasks). The cells were then cultured for 4-5 days at 27°C with 110rpm shaking. Expression of the protein was confirmed by SDS-PAGE and Western blotting using an anti penta-His monoclonal antibody (Qiagen) and was detected in the culture supernatant and cell lysate.

20 **Example 5****Purification of $\alpha_2\delta$ -2 deletion mutant of SEQ ID N°23**

The- $\alpha_2\delta$ -2 deletion mutant of SEQ ID N°23 was purified from the cell lysate following the purification strategy outlined below:

25 The culture was centrifuged at 6,000xg for 10 minutes and the supernatant removed. The weight of the cell pellet was determined before re-suspension in 20mM Tris pH8.0, 100mMKCl, 1% P40-Nonidet (100ml per 20g of wet cells). A protease inhibitor cocktail (Sigma, Cat# P8849), 1ml/L, was added to the mixture. The solution was then stirred for 10 minutes before centrifugation for 1hour at 30,000xg and 4°C. The supernatant was 30 concentrated (30kDa cut off) to approx. ~300ml then centrifuged for 1hour at 100,000xg.

Supernatant containing the soluble proteins was diluted 1:3 in 10mM Tris-HCl pH8.0 (equilibration buffer) and loaded onto a pre-equilibrated Q-Sepharose column (2.5cm i.d. x 30cm h.) at a flow rate of 900ml/h. After washing with equilibration buffer until a stable A_{280nm} baseline had been achieved, protein was eluted with 20mM Tris-HCl pH8.0, 0.5M KCl, 10mM Imidazole.

The eluate was then loaded onto a Ni-NTA (Qiagen) column (2.5cm i.d. x 6cm h.) pre-equilibrated in 20mM Tris pH8.0, 0.5M KCl, 10mM Imidazole at a flow rate of 2 ml/min. The column was washed successively with buffer A (20mM Tris pH8.0, 0.5M KCl, 20mM Imidazole), buffer B (100mM Tris-HCl pH8.0, 1M KCl), and buffer A again. Elution was performed with buffer C (20mM Tris-HCl pH8.0, 100mM KCl, 0.5M Imidazole). The Ni-NTA eluate (~50ml) was concentrated (30kDa cut-off) to ~2ml and applied at 1ml/min and in 0.2ml aliquots, to an FPLC Superdex-200 column equilibrated in 10mM HEPES, pH7.4, 150mM NaCl. Fractions containing the polypeptide of SEQ ID N°23 were pulled.

Example 6

SPA assay of [³H]gabapentin binding to the secreted soluble human $\alpha_2\delta$ -2 subunit of SEQ ID N°23

The assay is carried out at 21°C. Assay components are added in the following order (all reagents are diluted in 10mM HEPES (pH 7.4 at 21°C) to 96-well Optiplates:

25	25 μ l imidazole at various concentrations (diluted from a 1M stock pH8.0, see assay details)
25	50 μ l 10mM HEPES pH 7.4
	25 μ l (50mg) SPA beads (Amersham)
	100 μ l s- $\alpha_2\delta$ -2 subunit polypeptide of SEQ ID No 23 (2 μ l protein diluted to 100 μ l)
	25 μ l radioligand ([³ H]gabapentin obtained from example 5

Immediately after adding radioligand, the optiplates were loaded in the Packard Top Count scintillation counter to follow the binding time course. Imidazole was first used in the assay to optimize the specific interaction of the protein's 6His tag with the SPA bead. Imidazole itself (up to 100mM) in the filtration assay has no effect on [³H]gabapentin binding (n=1).

Example 7**Ni Flashplate assay of [³H]gabapentin binding to secreted soluble human $\alpha_2\delta$ -2 (SEQ ID N°23)**

Assays are carried out at 21°C in a final volume of 250µl in 96-well NEN Ni chelate

5 flash plates. Assay components are added in the following order (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

25µl 10mM HEPES pH7.4
25µl imidazole at various concentrations (diluted from a 1M stock pH8.0, see assay details)
10 75µl 10mM HEPES pH 7.4
100µl s- $\alpha_2\delta$ -2-6His (2µl protein diluted to 100µl) obtained from example 5
25µl radioligand ([³H]gabapentin (65Ci/mmol))

15 Immediately after adding the radioligand, flash plates are loaded in the Packard Top Count scintillation counter to follow the binding time course. The '[³H] flash plate' programme (cpm) is used to monitor activity. Imidazole is first used in the assay to optimize the specific interaction of the protein's 6His tag with the Ni flashplate.

20 **Example 8**

Ni Flashplate assay of [³H]Leucine binding to secreted soluble human $\alpha_2\delta$ -2-6His

The procedure described in example 7 is repeated, except that [³H]gabapentin is replaced by 25 µl (10.1 nM) of [³H]Leucine (141 Ci/mmol).

25

Example 9**Ni Flashplate assay studying competitive binding of [³H]gabapentin and (S+)-3-isobutyl GABA to human $\alpha_2\delta$ -2-6His (SEQ ID N°23).**

30 Assays are carried out at 21°C in a final volume of 250µl in 96-well NEN Ni chelate flash plates. Wells are set up for both 'total' and 'non-specific' binding. Specific binding is defined as that remaining after subtraction of the average of the 'non-specific binding' values from the average of the 'total' binding values. Assay components are added in the following order (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

35 25µl 10mM HEPES pH7.4 or 25 µl of the test compound at the appropriate concentration in HEPES

25 μ l 200 mM imidazole (diluted from a 1M stock pH8.0, see assay details)

Total binding 75 μ l 10mM HEPES pH 7.4

Non-specific binding 50 μ l 10mM HEPES pH 7.4 and 25 μ l 100 μ M (S+)-3-isobutyl GABA

5 100 μ l $\alpha_2\delta$ -2-6His (2 μ l protein* diluted to 100 μ l)

25 μ l radioligand ($[^3\text{H}]$ gabapentin or $[^3\text{H}]$ Leucine)

* The source of $\alpha_2\delta$ -2-6His is that purified by fplc Superdex-200 gel filtration (see 10 example 5)

Immediately after adding radioligand, flash plates are loaded in the Packard Top Count scintillation counter to follow the binding time course. Incubation time before the assay is 3 hours. The ' $[^3\text{H}]$ flash plate' programme (cpm) is used to monitor activity. Competition studies are compared across the flash-plate and filter binding methodologies. 15 in order to validate the new assay technology with the established filter binding methodology.

GraphPad Prism software is used to process competition curve data and determine IC_{50} and hill slope values. Twelve point competition curves with half log dilution steps of test 20 compounds are used in the experiments.

Example 10

Filter binding assay of $[^3\text{H}]$ gabapentin binding to the recombinant polypeptide of SEQ ID N°23

25 Assays were carried out at 21°C in a final volume of 250 μ l in 96-deep well plates. Assay components were (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

25 μ l compound to test

30 200 μ l Polypeptide of SEQ ID N°23 (3 μ l protein diluted to 200 μ l)

25 μ l radioligand ($[^3\text{H}]$ gabapentin (65Ci/mmmole)

Plates were incubated at room temperature for 1h prior to filtering on to 96-well GF/B Unifilter plates pre-soaked in 0.3% polyethylenimine. Filters were washed with 3x1ml 50mM Tris-HCl (pH 7.4 at 4°C), and dried over-night. Scintillant (Microscint O, 50 μ l) 35 was added and the plates counted using a Packard Top Count scintillation counter. Specific binding was ~98% of the 'total' value. In $[^3\text{H}]$ gabapentin saturation studies, the K_D (nM) obtained was about 10.62.

[³H]Gabapentin saturation studies.

Data shown represent the mean \pm SEM determined in 3 separate experiments. Saturation experiments were performed with 12 duplicate data points, [³H]gabapentin concentration

5 ranged from ~1-350nM. data was analysed using KEL-RADLIG

Human s- $\alpha_2\delta$ -2-6His

K_D in the filtration assay 28.55 ± 3.08 nM

10

Table 2

Binding affinities of key compounds in the [³H]gabapentin binding assay using s- $\alpha_2\delta$ -2-6His

Compound	K _i (nM) and range (n=3) Filtration assay
Gabapentin	20 (19-23)
(S+)-3-isobutyl GABA	11 (9.5-13)
(R)-3-isobutyl GABA	296 (282-310)

15 N.B. K_i=IC₅₀ / (1+[L]/K_D)

Competition curves were generated with 10 duplicate data points from 10 μ M to 1nM and analyzed on GraphPad prism.

20 **Example 11**

Binding of [³H]gabapentin to the recombinant polypeptide of SEQ ID N°23 using various flasplates assay formats and conditions

a) Preparation of protein stocks:

25 Protein was expressed as described in Example 4 except that the cells were infected at 1x10⁶ cells/ml. Additionally, the cells were cultured in 20 litre Applikon fermentation vessels (18L culture volume). The culture was maintained at 27°C and 60% dO₂ (100% dO₂ equates to [O₂] when media - without cells - has been saturated with air at 27°C) with single marine impeller stirring at 125rpm. The protein was expressed in either SF-30 900 II SFM (LTI Inc) or ESF-921 (Expression Systems Inc.) media.

b) Purification of s- $\alpha_2\delta$ -2-6His protein from cell culture supernatants:

On the harvest day (day 4-7 post-infection with virus) the cell culture was centrifuged at 9,000xg for 20 minutes to remove the cellular debris, and the supernatant concentrated to approximately 3 litres using a pellicon tangential-flow filtration system employing 10kDa cut-off cassettes. The concentrated sample was re-centrifuged at 9,000xg for 20 minutes then diluted with 2 volumes of 10mM Tris pH9.0. The diluted sample was then loaded at 10ml/min onto a Q-sepharose column (5cm i.d. x 50cm h.) which was washed with 20mM Tris-HCl (pH8.0) and eluted with 20mM Tris-HCl (pH8.0), 0.5M KCl, 10mM Imidazole.

5

10 The eluate was then loaded at 10ml/min onto a Ni-superflow (Qiagen) column (2.5cm i.d. x 6cm h.) pre-equilibrated in 20mM Tris (pH8.0), 0.1M KCl, 10mM Imidazole. The column was washed successively with buffer A (20mM Tris pH8.0, 0.5M KCl, 20mM Imidazole), 20mM Tris-HCl (pH8.0), 100mM KCl, and buffer A again at 10ml/min. Elution was performed with a gradient of buffer C (20mM Tris-HCl (pH8.0), 100mM KCl, 0.5M Imidazole) against buffer B at 2ml/min. Fractions from the gradient elution were assayed for [³H]gabapentin binding activity and the active fractions pooled then dialysed at 4°C four times (each for 24 hours) against 10mM HEPES, 150mM NaCl at a ratio of 1:60 (sample:dialysate). The dialysed material was then aliquoted and frozen for use in the assays as described below.

15

20

c) Preparation of protein cocktails for filter, wheat germ lectin and Ni chelate assays

(volumes in μ l):

25	cocktail	x1	x23		
		s- $\alpha_2\delta$ -2-6His	HBS	s- $\alpha_2\delta$ -2-6His	HBS
	0 μ l	0	75	0	1,725
	1 μ l	1	74	23	1,702
	2 μ l	2	73	46	1,679
30	4 μ l	4	71	92	1,633

s- $\alpha_2\delta$ -2-6His protein was sourced from the aliquots generated above.

d) Filter and Wheat Germ Lectin flashplate assays

35 The reagents were added in the following order to each well of either a 96-well Wheat Germ Lectin flashplate or a 96-deep well plate. Conditions were prepared in triplicate for both 'total' and 'non-specific' binding (20 μ l H₂O added for total binding and 20 μ l of

100µM (S+)-3-isobutyl GABA to define non-specific binding) for each of the four volumes of protein tested.

Assay set-up per well:

5

100µM (S+)-3-isobutyl GABA / H₂O 20µl
*100nM [³H]Gabapentin 20µl
235mM HEPES (pH7.3) 85µl
s- $\alpha_2\delta$ -2-6His (0, 1, 2 or 4µl - x23 cocktail) 75µl

10

* 20µl aliquots of the [³H]gabapentin stock added to each well were counted on a liquid β -scintillation counter (Beckman LS 5000TD) to determine the actual concentration of [³H]gabapentin achieved in each well. For these experiments this value was calculated as 10.8nM.

15

The Wheat Germ flashplate was then counted under continuous cycling conditions on a Packard Top Count Microplate scintillation counter. The plate was counted on the [³H]flashplate' programme with a count delay and count time of 1 minute. Data for the wheat germ lectin assay was plotted as 'specific' binding (i.e. 'total' minus 'non-specific binding'), see figure 3.

20

In the Filter assay, the binding reaction in the deep-well plate was left for 1 hour at 22°C then filtered with three 1ml washes of 4°C 50mM Tris (pH 7.4 at 4°C) onto a 96-well GF/B filter plate pre-soaked for 1 hour in 0.3% Polyethylenimine at 4°C. After leaving at 22°C to dry overnight 45µl of Microscint-O (Packard) was added to each filter well and the plate sealed and counted in the Packard Top Count Microplate Scintillation counter on the '[³H]Microscint' programme with a count delay and count time of 1 minute. The mean of the 'total' and 'non-specific' binding is presented in figure 1.

30

e) Nickel flashplate assay

2.35x Nickel flashplate buffer:

4.7ml 1M HEPES (pH7.3)

35

0.118ml 10% BSA (Sigma A7906, Fraction V (98%), Lot 57H1088) in H₂O

1.175ml 0.2M Imidazole pH7.3 (NaOH)

14.007ml H₂O

Assay set-up per well:

100 μ M (S+)-3-isobutyl GABA / H ₂ O	20 μ l
5 *100nM [³ H]Gabapentin	20 μ l
2.35x Nickel Flashplate buffer	85 μ l
s- α ₂ δ -2-6His (0, 1, 2 or 4 μ l of the x23 cocktail)	75 μ l

* 20 μ l aliquots of the [³H]gabapentin stock added to each well were counted on a liquid
10 β -scintillation counter (Beckman LS5000TD) to determine the actual concentration of [³H]gabapentin reached in the each well. For these experiments this value was calculated as 10.8nM.

15 The Nickel flashplate was then counted under continuous cycling conditions on the Packard Top Count Microplate scintillation counter. The plate was counted on the [³H]flashplate' programme with a count delay and count time of 1 minute (Figure 2).

20 The data described demonstrates that it is possible to assay [³H]gabapentin binding to recombinantly expressed freely soluble and purified s- α ₂ δ -2-6His in either a filter assay or an homogenous flashplate assay in either the Nickel chelate or the Wheat germ lectin format. The data demonstrates the extended stability of the flashplate assay over time, which is crucial if the assay format is to be used for mass-screening purposes, thus enabling the stacking of plates into counters (ideally with appropriate controls on each plate along with test compound wells in order to confirm signal stability across individual plates).

25 The data presented also demonstrate that it is possible to use the Wheat Germ lectin flashplate assay, as a primary assay or as a secondary screen to further refine and screen ligands identified or selected using the Ni flashplate assay or another format of this invention.

Example 12**Construction of a nucleotide sequence encoding a soluble secreted mouse $\alpha_2\delta$ -3 deletion mutant of SEQ ID N°24 as follows.**

5

a) Primer design

PCR primers were designed to generate the secreted soluble mouse $\alpha_2\delta$ -3 deletion mutant of SEQ ID N° 24 as follows:

5' PCR primer: This was designed to engineer in a KOZAK translation initiation

10 consensus sequence prior to the coding sequence (Kozak *JBC* 266 19867-19870)

3' PCR primer: This was designed to engineer in six histidine residues followed by a stop-codon at the desired location in the coding sequence. In addition to the stop codon the $\alpha_2\delta$ -3 primers also included an *Eco* RI restriction site.

15 The bold region in each primer sequence denotes the 'tagged' region; addition of sequences not present in the template. Primers were custom synthesized by Perkin Elmer Applied Biosystems UK to the ABI ready pure grade, supplied lyophilized then resuspended to 15 μ M in 10mM TE. JB201 and 202 were provided with 5' phosphate groups:

20

5' Primer JB201 (5'-TCGCCACCATGGCCGGGCCGGC-3', SEQ ID N°27)

3' Primer JB202 (5'-TCTCAGTGATGGTATGGTATGCGATGCACCCCCACACTCTC-3', SEQ ID N°28)

25

b) Protocol for PCR mediated 5' Kozak and 3' 6His tagging of mouse $\alpha_2\delta$ -3

30 The full length mouse $\alpha_2\delta$ -3 gene (Gen Bank Accession number AJ010949) in the pcDNA3 vector as described in Brown, J.P. and Gee, N.S., (Cloning and deletion mutagenesis of the $\alpha_2\delta$ calcium channel subunit from porcine cerebral cortex, *The journal of biological chemistry*, 273(39):25458-25465) was used as the template in the following PCR reaction.

The reagents were added in the following order in triplicate to a 96 well PCR plate:

35		μ l
	10x Pfx Amplification buffer	5
	10mM dNTPs	1.5

50mM MgSO ₄	1
15μM JB201	1.5
15μM JB202	1.5
100ng/μl pcDNA3-mouse-α ₂ δ-3	1
5 10x PCR Enhancer	5
H ₂ O	32.7
<u>2.5 UNITS/μL PFX POLYMERASE</u>	<u>0.8μL</u>

10 The plate was then cycled on an MJ Tetrad DNA engine according to the following cycling conditions:

94°C / 2mins

followed by:

for 30 cycles 94°C / 45sec

15 60°C / 45sec
68°C / 4mins

followed by:

68°C / 10mins

followed by:

20 hold at 4°C

The 3244bp product was then gel purified from a 1% TAE agarose gel using QIAEX beads and eluted in approximately 50μl.

25 The truncated protein of SEQ ID N°24 was expressed such the procedure of example 2,3 and 4.

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CLAIMS

1. A calcium channel $\alpha_2\delta$ subunit that is soluble and retains the functional characteristics of the full-length or wild-type $\alpha_2\delta$ subunit from which it derives.
- 5 2. A calcium channel $\alpha_2\delta$ subunit according to claim 1 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is of mammalian origin.
3. A calcium channel $\alpha_2\delta$ subunit according to claim 2 wherein the mammalian origin is a human, a porcine, a rat or a mouse origin.
4. A calcium channel $\alpha_2\delta$ subunit according to claim 3 wherein the mammalian origin is a human origin.
- 10 5. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 4, wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is naturally expressed in the cerebral cortical.
6. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 5, wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is voltage-dependent.
- 15 7. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 6, wherein the $\alpha_2\delta$ subunit is cleaved.
8. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 7, wherein the $\alpha_2\delta$ subunit is cleaved into separate α_2 and δ peptides.
9. A calcium channel $\alpha_2\delta$ subunit according to claim 8, wherein the α_2 and δ peptides are disulfide-bridged.
- 20 10. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 6, wherein the $\alpha_2\delta$ subunit is not cleaved.
11. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 10 characterized in that it is purified or isolated.
- 25 12. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 11 characterized in that it is processed as the full-length or wild-type $\alpha_2\delta$ subunit from which it derives is naturally processed.
13. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 12 characterized in that it is producable by the baculovirus/insect cells expression system.
- 30 14. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 13 characterized in that it is produced by the baculovirus/insect cells expression system.
15. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 14 characterized in that its δ peptide comprises at least the ligand-interacting part(s) of the complete δ peptide from which it originates
- 35 16. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 15 characterized in that its δ peptide has a C-terminal truncation with respect to the complete δ peptide

from which it originates, said truncation being sufficient to render the truncated δ peptide soluble.

17. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 16 characterized in that its α_2 peptide comprises at least the ligand-interacting part(s) of the complete α_2 peptide from which it originates.
18. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 15 or 17 characterized in that ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.
19. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 18 characterized in that its α_2 peptide comprises at least the ligand-interacting part(s) of the complete α_2 peptide from which it originates, its δ peptide comprises at least the ligand-interacting part(s) of the complete δ peptide from which it originates and its δ peptide does not comprise a part of the transmembrane domain of the complete δ peptide from which it originates which renders said calcium channel insoluble.
20. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 19 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates is $\alpha_2\delta$ -2, $\alpha_2\delta$ -3 or $\alpha_2\delta$ -4.
21. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 20 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°20.
22. A calcium channel $\alpha_2\delta$ subunit according to claim 20 or 21 characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 4, SEQ ID N° 5 or SEQ ID N° 6.
23. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20 to 22 characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 340 and amino acid number 1062 of SEQ ID N°20.
24. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 20 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°21.
25. A calcium channel $\alpha_2\delta$ subunit according to claim 20 or 24 characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 10, SEQ ID N° 11 or SEQ ID N° 12.
26. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20, 24 or 25 characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 306 and amino acid number 1019 of SEQ ID N°20.

27. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 20 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°55.

28. A calcium channel $\alpha_2\delta$ subunit according to claim 20 or 27 characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 53, SEQ ID N° 54 or SEQ ID N° 55.

29. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20, 27 or 28 characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1050 of SEQ ID N°55.

10 30. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 20 wherein the full-length or wild-type $\alpha_2\delta$ subunit from which it derives or originates has the amino acid sequence of SEQ ID N°33 or SEQ ID N°44.

15 31. A calcium channel $\alpha_2\delta$ subunit according to claim 20 or 30 characterized in that the amino acid sequence of its unprocessed form comprises or consists of SEQ ID N° 34, SEQ ID N° 35, SEQ ID N° 36, SEQ ID N° 41, SEQ ID N° 42 or SEQ ID N° 43.

32. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20, 30 or 31 characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1018 of SEQ ID N°33 or SEQ ID N°44.

20 33. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20, 30 or 31 characterized in that the amino acid sequence of its unprocessed form comprises or consists of the region comprised between amino acid number 302 and amino acid number 1018 of SEQ ID N°33 or SEQ ID N°44.

25 34. A calcium channel $\alpha_2\delta$ subunit according to any one of claims 20, 30, 31, 32 or 33 characterized in that its α_2 peptide comprises the region comprised between amino acid number 302 and amino acid number 946 or 997 of SEQ ID N°33 or of SEQ ID N°44 and its δ peptide comprises the region comprised between amino acid number 984 and amino acid number 1018 of SEQ ID N°33 or of SEQ ID N°44.

30 35. A calcium channel $\alpha_2\delta$ subunit characterized in that its α_2 peptide and its δ peptide have 99%, 98%, 97%, 96%, or 95% homology or identity with the α_2 peptide and the δ peptide respectively of a calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 34.

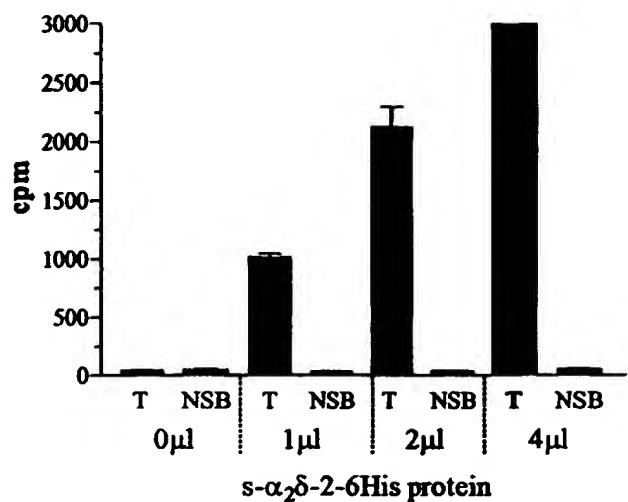
36. A nucleic acid molecule characterized in that its nucleotide sequence comprises a nucleotide sequence which encodes a calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 35.

35

37. A nucleic acid molecule characterized in that its nucleotide sequence comprises a nucleotide sequence which encodes the α_2 peptide or the δ peptide of a calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 35.
38. A nucleic acid molecule which hybridizes under stringent conditions with a nucleic acid molecule according to claim 36, 37 or 39.
39. A nucleic acid molecule according to any one of claims 36 to 38 which comprises SEQ ID N°1, SEQ ID N°2, SEQ ID N°3, SEQ ID N°7, SEQ ID N°8, SEQ ID N°9, SEQ ID N°13, SEQ ID N°14, SEQ ID N°15, SEQ ID N°30, SEQ ID N°31, SEQ ID N°32, SEQ ID N°38, SEQ ID N°39, SEQ ID N°40, SEQ ID N°50, SEQ ID N°51, or SEQ ID N°52.
40. A vector capable of expressing a nucleic acid molecule according to any one of claims 36 to 39.
41. An expression vector comprising a nucleic acid molecule according to any one of claims 36 to 39.
42. A vector according to claim 40 or 41 which is a baculovirus vector.
43. A cell comprising a nucleic acid molecule according to any one of claims 36 to 39.
44. A cell comprising a vector according to claim 40, 41 or 42.
45. A cell according to claim 43 or 44 which is a mammalian cell or an insect cell.
46. A composition comprising a calcium channel $\alpha_2\delta$ subunit according to any one of claims 7 to 9 and a calcium channel $\alpha_2\delta$ subunit according to claim 10.
47. Screening assay using a calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 35.
48. Screening assay according to claim 47 which is an SPA assay, a Flashplate assay, a Nickel Flasplate assay, a Filter binding assay or a Wheat Germ Lectin flasplate assay.
49. Use of screening assay according to claim 47 or 48 to detect or measure the binding or interaction of a ligand of a calcium channel $\alpha_2\delta$ subunit and a calcium channel $\alpha_2\delta$ subunit.
50. Use according to claim 49 wherein the ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.
51. Kit to detect or measure the binding or interaction of a ligand of a calcium channel $\alpha_2\delta$ subunit and a calcium channel $\alpha_2\delta$ subunit comprising a calcium channel $\alpha_2\delta$ subunit according to any one of claims 1 to 35.
52. Kit according to claim 51 wherein the ligand is gabapentin, L-Norleucine, L-Allo-Isoleucine, L-Methionine, L-Leucine, L-Isoleucine, L-Valine, Spermine or L-Phenylalanine.

53. Kit according to claim 51 or 52 usable in an SPA assay, a Flashplate assay, a Nick~~ed~~
Flasplate assay, a Filter binding assay or a Wheat Germ Lectin flasplate assay.

Figure 1



T -Total Binding
NSB -Non-Specific Binding

Figure 2

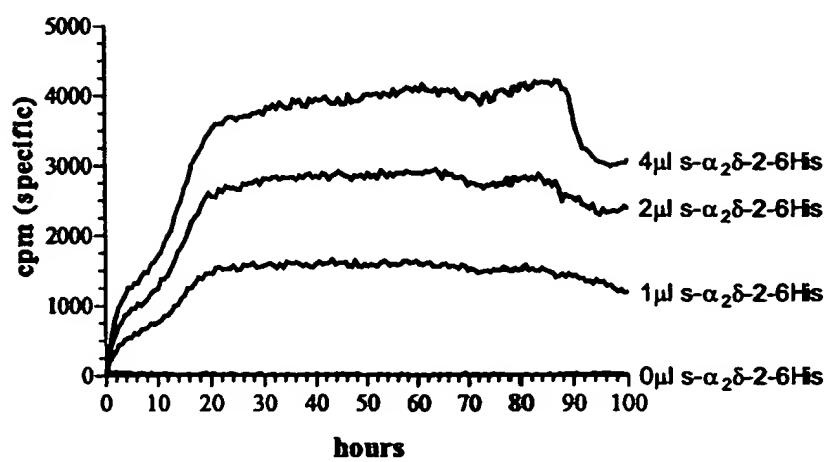
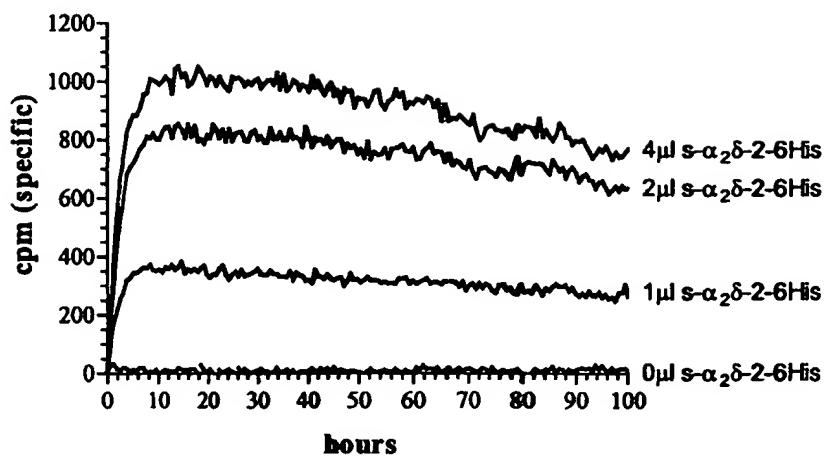


Figure 3



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	1025	1030	1035
	Thr Asn Thr Asn Leu Leu Phe Val Val Ala Glu Lys Pro Leu Cys Ser		
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Tyr Tyr Asp Ala Lys Ala Asp Ala Glu Leu Asp Asp Pro Glu Ser Glu
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40 Asp Val Glu Arg Gly Ser Lys Ala Ser Thr Leu Arg Leu Asp Phe Ile
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Glu Asp Pro Asn Phe Lys Asn Lys Val Asn Tyr Ser Tyr Ala Ala Val
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Gln Ile Pro Thr Asp Ile Tyr Lys Gly Ser Thr Val Ile Leu Asn Glu
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Leu Tyr Asp Val Arg Arg Pro Trp Tyr Ile Gln Gly Ala Ser Ser

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	Leu Ser Asp Asp Asp Tyr Val Asn Val Ala Ser Phe Asn Glu Lys Ala		
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	Gln Pro Val Ser Cys Phe Thr His Leu Val Gln Ala Asn Val Arg Asn		
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	Thr Gly Tyr Lys Ala Gly Phe Glu Tyr Ala Phe Asp Gln Leu Gln Asn		
	370	375	380
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	Asp Gly Gly Glu Asp Arg Val Gln Asp Val Phe Glu Lys Tyr Asn Trp		
25	405	410	415
	Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn		
	420	425	430
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	Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu		
	450	455	460
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	Asn Gln Val Gln Trp Thr Asn Val Tyr Glu Asp Ala Leu Gly Leu Gly		
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	Leu Val Val Thr Gly Thr Leu Pro Val Phe Asn Leu Thr Gln Asp Gly		
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	His Pro Asn Leu Lys Pro Gln Thr Thr Asn Phe Arg Glu Pro Val Thr		
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	Leu Asp Phe Leu Asp Ala Glu Leu Glu Asp Glu Asn Lys Glu Glu Ile		
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 Asn Ala Ser Asp Asn Asn Thr Glu Phe Leu Lys Asn Phe Ile Glu Leu
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 Met Glu Lys Val Thr Pro Asp Ser Lys Gln Cys Asn Asn Phe Leu Leu
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 Glu Asp Trp Thr Glu Asn Pro Glu Pro Phe Asn Ala Ser Phe Tyr Arg
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 45 Ala Val Val Gly Val Lys Leu Asp Leu Glu Ala Trp Ala Glu Lys Phe
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 50 850 855 860
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 865 870 875 880
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5 Glu Ser Tyr Asp Tyr Gln Ala Ala Cys Ala Pro Gln Pro Pro Gly Asn
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Pro Gln Gln His Thr Met Gln His Trp Ala Arg Arg Leu Glu Gln Glu
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Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn
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5 Tyr Asp Val Thr Pro Leu Gln Trp Met Ala Cys Ala Asn Lys Gly Tyr
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Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu
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	aacctgttca	tggtggtgtt	ggacagcagc	tgcctctgtg	aatctgtgge	ccccatcacc	3060
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 tccggttccc agcttctgca aaagaataac aaagagtatg agaaaagacgt tgccatagaa 240
 gaaattgatg gcctccaact ggtaaaagaag ctggcaaaaga acatggaaga gatgtttcac 300
 30 aagaagtctg aggccgtcag gctgtgtt gaggctgcag aagaagcaca cctgaaacat 360
 gaatttgatg cagacttaca gtatgaatac ttcaatgtcg tgctgataaa taaaaggac 420
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 aataatttgc ctgtgaacat cagtcataatg gacgtccaag taccacgaa catgtacaac 540
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 gataacttg accgtgaccc atctctcata tggcagttact ttggaaagtgc aaagggttt 660
 35 tttaggcagt atccggggat taaatggaa ccagatgaga atggagtcat tgccttcgac 720
 tgcaggaacc gaaaatgta catccaggca gcaacttctc cggaaagacgt ggtcatttt 780
 gttgaegtca gtggcagcat gaaaggactc cgtctgacta tgcgcaagca aacagtctca 840
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 cttaactatg tggAACCTT cctgtatggaa actttggtgc aagccgacag gacaaacaaa 960
 40 gagcaactca gggagcatct ggacaaactt ttcgccaagaa gaattggaaat gttggatata 1020
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 gctgegtttg cagacaatct aaagtggatg gctgtgcca acaaaggatt tttaacccag 1260
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 acagacatca agggtaactcc ttctagtttgc ggtgtggcgc ttccagagg tcatggaaa 1860
 55 tatttcctcc gagggaaatgt aaccatcgaa gaaggcctgc atgactttaga acatcccgt 1920
 gtgtccctgg cagatgaatg gtccactgtc aacactgacc tacacccctga gcacccgcat 1980
 ctgtctcagt tagaagcgat taagctctac ctaaaaggca aagaacctt gctccagttgt 2040
 gataaaagaat tgatccaaga agtcttttttgc gacgcgggtgg tgagtgeccc cattgaagcg 2100
 tattggacca qccctqqccct caacaaatct qaaaattctg acaaaaggcgt qqqqqtttggcc 2160

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 aacaatgtc taacaatggg ttcccttaaa agaattaccc ttatgacta ccaagccatg 2700
 10 ttttaggcca acaaggaaag cagcgatggc gcccattggcc ttctggatcc ttataatgcc 2760
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 gggatattt ctgtgaaga ctgttccaaat tttttgttca tccagcaat cccaaaggcage 3000
 15 aacctgttca tttttgttggg ggacagcage tttttgttca aatctgtggc ccccatcacc 3060
 atggcaccca ttgaaatcg gtataatgaa tcccttaagt gtgaacgtct aaaggccag 3120
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 <212> PRT
 <213> Homo sapiens

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30 Leu Leu Ala Ala Ala Leu Leu Tyr Ala Ala Leu Gly Asp Val Val Arg
 20 25 30

Ser Glu Gln Gln Ile Pro Leu Ser Val Val Lys Leu Trp Ala Ser Ala
 35 40 45

35 Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln
 50 55 60

Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
 40 65 70 75 80

Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Asn Met Glu
 85 90 95

45 Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
 100 105 110

Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
 115 120 125

50 Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
 130 135 140

Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe
 55 145 150 155 160

Asn Asn Leu Pro Val Asn Ile Ser Leu Ser Asp Val Gln Val Pro Thr
 165 170 175

Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
 180 185 190
 5 Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
 195 200 205
 Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
 210 215 220
 10 Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp
 225 230 235 240
 Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp
 245 250 255
 15 Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu
 260 265 270
 Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp
 20 275 280 285
 Asp Asp Phe Phe Asn Ile Ile Ala Tyr Asn Glu Glu Leu His Tyr Val
 290 295 300
 25 Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys
 305 310 315 320
 Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly
 325 330 335
 30 Met Leu Asp Ile Ala Leu Asn Glu Ala Phe Asn Ile Leu Ser Asp Phe
 340 345 350
 Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile
 35 355 360 365
 Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn
 370 375 380
 40 Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu
 385 390 395 400
 Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly
 405 410 415
 45 Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met
 420 425 430
 Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His
 50 435 440 445
 Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Thr Asp Asp
 450 455 460
 55 Gln Gly Pro Val Leu Met Thr Thr Val Ala Met Pro Val Phe Ser Lys
 465 470 475 480
 Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu Leu Gly Val Val Gly Thr
 485 490 495

Asp Val Pro Val Lys Glu Leu Leu Lys Thr Ile Pro Lys Tyr Lys Leu
 500 505 510

5 Gly Ile His Gly Tyr Ala Phe Ala Ile Thr Asn Asn Gly Tyr Ile Leu
 515 520 525

Thr His Pro Glu Leu Arg Leu Leu Tyr Glu Glu Gly Lys Lys Arg Arg
 530 535 540

10 Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser Glu Val Glu Trp Glu Asp
 545 550 555 560

Arg Asp Asp Val Leu Arg Asn Ala Met Val Asn Arg Lys Thr Gly Lys
 15 565 570 575

Phe Ser Met Glu Val Lys Lys Thr Val Asp Lys Gly Lys Arg Val Leu
 580 585 590

20 Val Met Thr Asn Asp Tyr Tyr Tyr Thr Asp Ile Lys Gly Thr Pro Phe
 595 600 605

Ser Leu Gly Val Ala Leu Ser Arg Gly His Gly Lys Tyr Phe Phe Arg
 610 615 620

25 Gly Asn Val Thr Ile Glu Glu Gly Leu His Asp Leu Glu His Pro Asp
 625 630 635 640

Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys Asn Thr Asp Leu His Pro
 30 645 650 655

Glu His Arg His Leu Ser Gln Leu Glu Ala Ile Lys Leu Tyr Leu Lys
 660 665 670

35 Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys Glu Leu Ile Gln Glu Val
 675 680 685

Leu Phe Asp Ala Val Val Ser Ala Pro Ile Glu Ala Tyr Trp Thr Ser
 690 695 700

40 Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp Lys Gly Val Glu Val Ala
 705 710 715 720

Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg Ile Asn Leu Phe Val Gly
 45 725 730 735

Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu Lys Ala Gly Asp Lys Glu
 740 745 750

50 Asn Ile Phe Asn Ala Asp His Phe Pro Leu Trp Tyr Arg Arg Ala Ala
 755 760 765

Glu Gln Ile Pro Gly Ser Phe Val Tyr Ser Ile Pro Phe Ser Thr Gly
 770 775 780

55 Pro Val Asn Lys Ser Asn Val Val Thr Ala Ser Thr Ser Ile Gln Leu
 785 790 795 800

Leu Asp Glu Arg Lys Ser Pro Val Val Ala Ala Val Gly Ile Gln Met

	805	810	815
	Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp Thr Ala Ser Arg Gln Cys		
	820	825	830
5	Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser Cys Asp Asp Glu Thr Val		
	835	840	845
10	Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe Ile Leu Val Ser Glu Asp		
	850	855	860
	Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu Ile Glu Gly Ala Val Met		
	865	870	875
15	Asn Lys Leu Leu Thr Met Gly Ser Phe Lys Arg Ile Thr Leu Tyr Asp		
	885	890	895
	Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu Ser Ser Asp Gly Ala His		
	900	905	910
20	Gly Leu Leu Asp Pro Tyr Asn Ala Phe Leu Ser Ala Val Lys Trp Ile		
	915	920	925
25	Met Thr Glu Leu Val Leu Phe Leu Val Glu Phe Asn Leu Cys Ser Trp		
	930	935	940
	Trp His Ser Asp Met Thr Ala Lys Ala Gln Lys Leu Lys Gln Thr Leu		
	945	950	955
30	Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe Val Ser Glu Arg Thr Ile		
	965	970	975
	Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu Asp Cys Ser Lys Ser Phe		
	980	985	990
35	Val Ile Gln Gln Ile Pro Ser Ser Asn Leu Phe Met Val Val Val Asp		
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	Ser Ser Cys Leu Cys Glu Ser Val Ala Pro Ile		
40	1010	1015	
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45	<212> PRT		
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	<400> 11		
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	Leu Leu Ala Ala Ala Leu Leu Tyr Ala Ala Leu Gly Asp Val Val Arg		
	20	25	30
55	Ser Glu Gln Gln Ile Pro Leu Ser Val Val Lys Leu Trp Ala Ser Ala		
	35	40	45
	Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln		
	50	55	60

Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
 65 70 75 80

5 Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Asn Met Glu
 85 90 95

Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
 100 105 110

10 Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
 115 120 125

15 Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
 130 135 140

Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe
 145 150 155 160

20 Asn Asn Leu Pro Val Asn Ile Ser Leu Ser Asp Val Gln Val Pro Thr
 165 170 175

Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
 180 185 190

25 Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
 195 200 205

30 Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
 210 215 220

Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp
 225 230 235 240

35 Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp
 245 250 255

Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu
 260 265 270

40 Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp
 275 280 285

Asp Asp Phe Phe Asn Ile Ile Ala Tyr Asn Glu Glu Leu His Tyr Val
 290 295 300

45 Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys
 305 310 315 320

50 Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly
 325 330 335

Met Leu Asp Ile Ala Leu Asn Glu Ala Phe Asn Ile Leu Ser Asp Phe
 340 345 350

55 Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile
 355 360 365

Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn

	370	375	380
	Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu		
385	390	395	400
5	Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly		
	405	410	415
10	Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met		
	420	425	430
	Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His		
	435	440	445
15	Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Thr Asp Asp		
	450	455	460
	Gln Gly Pro Val Leu Met Thr Thr Val Ala Met Pro Val Phe Ser Lys		
	465	470	475
20	Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu Leu Gly Val Val Gly Thr		
	485	490	495
	Asp Val Pro Val Lys Glu Leu Leu Lys Thr Ile Pro Lys Tyr Lys Leu		
25	500	505	510
	Gly Ile His Gly Tyr Ala Phe Ala Ile Thr Asn Asn Gly Tyr Ile Leu		
	515	520	525
30	Thr His Pro Glu Leu Arg Leu Leu Tyr Glu Glu Gly Lys Lys Arg Arg		
	530	535	540
	Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser Glu Val Glu Trp Glu Asp		
	545	550	555
35	Arg Asp Asp Val Leu Arg Asn Ala Met Val Asn Arg Lys Thr Gly Lys		
	565	570	575
	Phe Ser Met Glu Val Lys Lys Thr Val Asp Lys Gly Lys Arg Val Leu		
40	580	585	590
	Val Met Thr Asn Asp Tyr Tyr Thr Asp Ile Lys Gly Thr Pro Phe		
	595	600	605
45	Ser Leu Gly Val Ala Leu Ser Arg Gly His Gly Lys Tyr Phe Phe Arg		
	610	615	620
	Gly Asn Val Thr Ile Glu Glu Gly Leu His Asp Leu Glu His Pro Asp		
	625	630	635
50	640	645	650
	Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys Asn Thr Asp Leu His Pro		
	655	660	665
	Glu His Arg His Leu Ser Gln Leu Glu Ala Ile Lys Leu Tyr Leu Lys		
55	670	675	680
	Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys Glu Leu Ile Gln Glu Val		
	685		

Leu Phe Asp Ala Val Val Ser Ala Pro Ile Glu Ala Tyr Trp Thr Ser
 690 695 700
 Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp Lys Gly Val Glu Val Ala
 5 705 710 715 720
 Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg Ile Asn Leu Phe Val Gly
 725 730 735
 10 Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu Lys Ala Gly Asp Lys Glu
 740 745 750
 Asn Ile Phe Asn Ala Asp His Phe Pro Leu Trp Tyr Arg Arg Ala Ala
 755 760 765
 15 Glu Gln Ile Pro Gly Ser Phe Val Tyr Ser Ile Pro Phe Ser Thr Gly
 770 775 780
 Pro Val Asn Lys Ser Asn Val Val Thr Ala Ser Thr Ser Ile Gln Leu
 20 785 790 795 800
 Leu Asp Glu Arg Lys Ser Pro Val Val Ala Ala Val Gly Ile Gln Met
 805 810 815
 25 Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp Thr Ala Ser Arg Gln Cys
 820 825 830
 Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser Cys Asp Asp Glu Thr Val
 835 840 845
 30 Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe Ile Leu Val Ser Glu Asp
 850 855 860
 Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu Ile Glu Gly Ala Val Met
 35 865 870 875 880
 Asn Lys Leu Leu Thr Met Gly Ser Phe Lys Arg Ile Thr Leu Tyr Asp
 885 890 895
 40 Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu Ser Ser Asp Gly Ala His
 900 905 910
 Gly Leu Leu Asp Pro Tyr Asn Ala Phe Leu Ser Ala Val Lys Trp Ile
 915 920 925
 45 Met Thr Glu Leu Val Leu Phe Leu Val Glu Phe Asn Leu Cys Ser Trp
 930 935 940
 Trp His Ser Asp Met Thr Ala Lys Ala Gln Lys Leu Lys Gln Thr Leu
 50 945 950 955 960
 Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe Val Ser Glu Arg Thr Ile
 965 970 975
 55 Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu Asp Cys Ser Lys Ser Phe
 980 985 990
 Val Ile Gln Gln Ile Pro Ser Ser Asn Leu Phe Met Val Val Val Asp
 995 1000 1005

Ser Ser Cys Leu Cys Glu Ser Val Ala Pro Ile Thr Met Ala Pro Ile
 1010 1015 1020

5 Glu Ile Arg Tyr Asn Glu Ser Leu Lys Cys Glu Arg Leu Lys
 1025 1030 1035

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 <212> PRT
 <213> Homo sapiens

15 <400> 12
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Leu Leu Ala Ala Ala Leu Leu Tyr Ala Ala Leu Gly Asp Val Val Arg
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20 Ser Glu Gln Gln Ile Pro Leu Ser Val Val Lys Leu Trp Ala Ser Ala
 35 40 45

25 Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln
 50 55 60

Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
 65 70 75 80

30 Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Asn Met Glu
 85 90 95

Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
 100 105 110

35 Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
 115 120 125

Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
 40 130 135 140

Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe
 145 150 155 160

45 Asn Asn Leu Pro Val Asn Ile Ser Leu Ser Asp Val Gln Val Pro Thr
 165 170 175

Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
 180 185 190

50 Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
 195 200 205

Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
 55 210 215 220

Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp
 225 230 235 240

Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp
 245 250 255
 Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu
 5 260 265 270
 Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp
 275 280 285
 10 Asp Asp Phe Phe Asn Ile Ile Ala Tyr Asn Glu Glu Leu His Tyr Val
 290 295 300
 Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys
 305 310 315 320
 15 Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly
 325 330 335
 Met Leu Asp Ile Ala Leu Asn Glu Ala Phe Asn Ile Leu Ser Asp Phe
 20 340 345 350
 Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile
 355 360 365
 25 Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn
 370 375 380
 Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu
 385 390 395 400
 30 Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly
 405 410 415
 Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met
 35 420 425 430
 Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His
 435 440 445
 40 Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Thr Asp Asp
 450 455 460
 Gln Gly Pro Val Leu Met Thr Thr Val Ala Met Pro Val Phe Ser Lys
 465 470 475 480
 45 Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu Leu Gly Val Val Gly Thr
 485 490 495
 Asp Val Pro Val Lys Glu Leu Leu Lys Thr Ile Pro Lys Tyr Lys Leu
 50 500 505 510
 Gly Ile His Gly Tyr Ala Phe Ala Ile Thr Asn Asn Gly Tyr Ile Leu
 515 520 525
 55 Thr His Pro Glu Leu Arg Leu Leu Tyr Glu Glu Gly Lys Lys Arg Arg
 530 535 540
 Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser Glu Val Glu Trp Glu Asp
 545 550 555 560

Arg Asp Asp Val Leu Arg Asn Ala Met Val Asn Arg Lys Thr Gly Lys
 565 570 575

5 Phe Ser Met Glu Val Lys Lys Thr Val Asp Lys Gly Lys Arg Val Leu
 580 585 590

Val Met Thr Asn Asp Tyr Tyr Thr Asp Ile Lys Gly Thr Pro Phe
 595 600 605

10 Ser Leu Gly Val Ala Leu Ser Arg Gly His Gly Lys Tyr Phe Phe Arg
 610 615 620

Gly Asn Val Thr Ile Glu Glu Gly Leu His Asp Leu Glu His Pro Asp
 15 625 630 635 640

Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys Asn Thr Asp Leu His Pro
 645 650 655

20 Glu His Arg His Leu Ser Gln Leu Glu Ala Ile Lys Leu Tyr Leu Lys
 660 665 670

Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys Glu Leu Ile Gln Glu Val
 675 680 685

25 Leu Phe Asp Ala Val Val Ser Ala Pro Ile Glu Ala Tyr Trp Thr Ser
 690 695 700

Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp Lys Gly Val Glu Val Ala
 30 705 710 715 720

Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg Ile Asn Leu Phe Val Gly
 725 730 735

35 Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu Lys Ala Gly Asp Lys Glu
 740 745 750

Asn Ile Phe Asn Ala Asp His Phe Pro Leu Trp Tyr Arg Arg Ala Ala
 755 760 765

40 Glu Gln Ile Pro Gly Ser Phe Val Tyr Ser Ile Pro Phe Ser Thr Gly
 770 775 780

Pro Val Asn Lys Ser Asn Val Val Thr Ala Ser Thr Ser Ile Gln Leu
 45 785 790 795 800

Leu Asp Glu Arg Lys Ser Pro Val Val Ala Ala Val Gly Ile Gln Met
 805 810 815

50 Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp Thr Ala Ser Arg Gln Cys
 820 825 830

Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser Cys Asp Asp Glu Thr Val
 835 840 845

55 Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe Ile Leu Val Ser Glu Asp
 850 855 860

Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu Ile Glu Gly Ala Val Met

865	870	875	880
Asn Lys Leu Leu Thr Met Gly Ser Phe Lys Arg Ile Thr Leu Tyr Asp			
885	890	895	
5 Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu Ser Ser Asp Gly Ala His			
900	905	910	
10 Gly Leu Leu Asp Pro Tyr Asn Ala Phe Leu Ser Ala Val Lys Trp Ile			
915	920	925	
15 Met Thr Glu Leu Val Leu Phe Leu Val Glu Phe Asn Leu Cys Ser Trp			
930	935	940	
20 Trp His Ser Asp Met Thr Ala Lys Ala Gln Lys Leu Lys Gln Thr Leu			
945	950	955	960
Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe Val Ser Glu Arg Thr Ile			
965	970	975	
25 Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu Asp Cys Ser Lys Ser Phe			
980	985	990	
30 Val Ile Gln Gln Ile Pro Ser Ser Asn Leu Phe Met Val Val Val Asp			
995	1000	1005	
35 Ser Ser Cys Leu Cys Glu Ser Val Ala Pro Ile Thr Met Ala Pro Ile			
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40 Glu Ile Arg Tyr Asn Glu Ser Leu Lys Cys Glu Arg Leu Lys Ala Gln			
1025	1030	1035	1040
Lys Ile Arg Arg Pro Glu Ser Cys His Gly Phe His Pro Glu Glu			
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 15 aagaggacag ccattgtcgc agccgcgggc gtccaaatga agcttggaaatt cctccagcgc 300
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 10 35 40 45
 Ser Phe Val Phe Asn Leu Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly
 50 55 60
 15 Glu Pro Met Val Val Thr Ala Ser Thr Ala Val Ala Val Thr Val Asp
 65 70 75 80
 Lys Arg Thr Ala Ile Ala Ala Ala Gly Val Gln Met Lys Leu Glu
 85 90 95
 20 Phe Leu Gln Arg Lys Phe Trp Ala Ala Thr Arg Gln Cys Ser Thr Val
 100 105 110
 Asp Gly Pro Cys Thr Gln Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe
 25 115 120 125
 Val Ile Asp Asn Asn Gly Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu
 130 135 140
 30 Thr Gly Arg Phe Leu Gly Glu Val Asp Gly Ala Val Leu Thr Gln Leu
 145 150 155 160
 Leu Ser Met Gly Val Phe Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala
 165 170 175
 35 Met Cys Lys Pro Ser Ser His His Ser Ala Ala Gln Pro Leu Val
 180 185 190
 Ser Pro Ile Ser Ala Phe Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu
 40 195 200 205
 Leu Val Leu Phe Leu Leu Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp
 210 215 220
 45 Arg Gly Ala Glu Ala Lys Ser Val Phe His His Ser His Lys His Lys
 225 230 235 240
 Lys Gln Asp Pro Leu Gln Pro Cys Asp Thr Glu Tyr Pro Val Phe Val
 245 250 255
 50 Tyr Gln Pro Ala Ile Arg Glu Ala Asn Gly Ile Val Glu Cys Gly Pro
 260 265 270
 Cys Gln Lys Val Phe Val Val Gln Gln Ile Pro Asn Ser Asn Leu Leu
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Asp Arg Phe Pro Leu Trp Tyr Arg Gln Ala Ser Glu His Pro Ala Gly
35 40 45

20 Ser Phe Val Phe Asn Leu Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly
50 55 60

Glu Pro Met Val Val Thr Ala Ser Thr Ala Val Ala Val Thr Val Asp
65 70 75 80

25 Lys Arg Thr Ala Ile Ala Ala Ala Gly Val Gln Met Lys Leu Glu
85 90 95

30 Phe Leu Gln Arg Lys Phe Trp Ala Ala Thr Arg Gln Cys Ser Thr Val
100 105 110

Asp Gly Pro Cys Thr Gln Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe
115 120 125

35 Val Ile Asp Asn Asn Gly Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu
130 135 140

Thr Gly Arg Phe Leu Gly Glu Val Asp Gly Ala Val Leu Thr Gln Leu
145 150 155 160

40 Leu Ser Met Gly Val Phe Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala
165 170 175

Met Cys Lys Pro Ser Ser His His Ser Ala Ala Gln Pro Leu Val
45 180 185 190

Ser Pro Ile Ser Ala Phe Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu
195 200 205

50 Leu Val Leu Phe Leu Leu Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp
210 215 220

Arg Gly Ala Glu Ala Lys Ser Val Phe His His Ser His Lys His Lys
225 230 235 240

55 Lys Gln Asp Pro Leu Gln Pro Cys Asp Thr Glu Tyr Pro Val Phe Val
245 250 255

Tyr Gln Pro Ala Ile Arg Glu Ala Asn Gly Ile Val Glu Cys Gly Pro

	260	265	270
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	Leu Leu Val Thr Asp Pro Thr Cys Asp Cys Ser Ile Phe Pro Pro Val 290	295	300
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30	Ser Phe Val Phe Asn Leu Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly 50 55 60		
35	Glu Pro Met Val Val Thr Ala Ser Thr Ala Val Ala Val Thr Val Asp 65 70 75 80		
	Lys Arg Thr Ala Ile Ala Ala Ala Gly Val Gln Met Lys Leu Glu 85 90 95		
40	Phe Leu Gln Arg Lys Phe Trp Ala Ala Thr Arg Gln Cys Ser Thr Val 100 105 110		
	Asp Gly Pro Cys Thr Gln Ser Cys Glu Asp Ser Asp Leu Asp Cys Phe 115 120 125		
45	Val Ile Asp Asn Asn Gly Phe Ile Leu Ile Ser Lys Arg Ser Arg Glu 130 135 140		
	Thr Gly Arg Phe Leu Gly Glu Val Asp Gly Ala Val Leu Thr Gln Leu 145 150 155 160		
50	Leu Ser Met Gly Val Phe Ser Gln Val Thr Met Tyr Asp Tyr Gln Ala 165 170 175		
55	Met Cys Lys Pro Ser Ser His His His Ser Ala Ala Gln Pro Leu Val 180 185 190		
	Ser Pro Ile Ser Ala Phe Leu Thr Ala Thr Arg Trp Leu Leu Gln Glu 195 200 205		

Leu Val Leu Phe Leu Leu Glu Trp Ser Val Trp Trp Gly Ser Trp Tyr Asp
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 5 Arg Gly Ala Glu Ala Lys Ser Val Phe His His Ser His Lys His Lys
 225 230 235 240
 Lys Gln Asp Pro Leu Gln Pro Cys Asp Thr Glu Tyr Pro Val Phe Val
 245 250 255
 10 Tyr Gln Pro Ala Ile Arg Glu Ala Asn Gly Ile Val Glu Cys Gly Pro
 260 265 270
 Cys Gln Lys Val Phe Val Val Gln Gln Ile Pro Asn Ser Asn Leu Leu
 15 275 280 285
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 290 295 300
 20 Leu Gln Glu Ala Thr Glu Val Lys Tyr Asn Ala Ser Val Lys Cys Asp
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 25 35 40 45

Pro Leu Leu Pro Leu Leu Ala Ala Pro Gly Ala Ser Ala Tyr Ser Phe
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30 Pro Gln Gln His Thr Met Gln His Trp Ala Arg Arg Leu Glu Gln Glu
 65 70 75 80

Val Asp Gly Val Met Arg Ile Phe Gly Gly Val Gln Gln Leu Arg Glu
 85 90 95

35 Ile Tyr Lys Asp Asn Arg Asn Leu Phe Glu Val Gln Glu Asn Glu Pro
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Gln Lys Leu Val Glu Lys Val Ala Gly Asp Ile Glu Ser Leu Leu Asp
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Arg Lys Val Gln Ala Leu Lys Arg Leu Ala Asp Ala Ala Glu Asn Phe
 130 135 140

45 Gln Lys Ala His Arg Trp Gln Asp Asn Ile Lys Glu Glu Asp Ile Val
 145 150 155 160

Tyr Tyr Asp Ala Lys Ala Asp Ala Glu Leu Asp Asp Pro Glu Ser Glu
 165 170 175

50 Asp Val Glu Arg Gly Ser Lys Ala Ser Thr Leu Arg Leu Asp Phe Ile
 180 185 190

Glu Asp Pro Asn Phe Lys Asn Lys Val Asn Tyr Ser Tyr Ala Ala Val
 55 195 200 205

Gln Ile Pro Thr Asp Ile Tyr Lys Gly Ser Thr Val Ile Leu Asn Glu
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 260 265 270
 10 Leu Tyr Asp Val Arg Arg Arg Pro Trp Tyr Ile Gln Gly Ala Ser Ser
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 15 Leu Thr Leu Lys Leu Met Lys Thr Ser Val Cys Glu Met Leu Asp Thr
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 25 Lys Lys Val Phe Lys Glu Ala Val Gln Gly Met Val Ala Lys Gly Thr
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 Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn
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 40 Tyr Asp Val Thr Pro Leu Gln Trp Met Ala Cys Ala Asn Lys Gly Tyr
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 Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu
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 45 Tyr Leu Asp Val Leu Gly Arg Pro Met Val Leu Ala Gly Lys Glu Ala
 465 470 475 480
 Lys Gln Val Gln Trp Thr Asn Val Tyr Glu Asp Ala Leu Gly Leu Gly
 50 485 490 495
 Leu Val Val Thr Gly Thr Leu Pro Val Phe Asn Leu Thr Gln Asp Gly
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 55 Pro Gly Glu Lys Lys Asn Gln Leu Ile Leu Gly Val Met Gly Ile Asp
 515 520 525
 Val Ala Leu Asn Asp Ile Lys Arg Leu Thr Pro Asn Tyr Thr Leu Gly
 530 535 540

Ala Asn Gly Tyr Val Phe Ala Ile Asp Leu Asn Gly Tyr Val Leu Leu
 545 550 555 560

5 His Pro Asn Leu Lys Pro Gln Thr Thr Asn Phe Arg Glu Pro Val Thr
 565 570 575

Leu Asp Phe Leu Asp Ala Glu Leu Glu Asp Glu Asn Lys Glu Glu Ile
 580 585 590

10 Arg Arg Ser Met Ile Asp Gly Asn Lys Gly His Lys Gln Ile Arg Thr
 595 600 605

Leu Val Lys Ser Leu Asp Glu Arg Tyr Ile Asp Glu Val Thr Arg Asn
 15 610 615 620

Tyr Thr Trp Val Pro Ile Arg Ser Thr Asn Tyr Ser Leu Gly Leu Val
 625 630 635 640

20 Leu Pro Pro Tyr Ser Thr Phe Tyr Leu Gln Ala Asn Leu Ser Asp Gln
 645 650 655

Ile Leu Gln Val Lys Tyr Phe Glu Phe Leu Leu Pro Ser Ser Phe Glu
 660 665 670

25 Ser Glu Gly His Val Phe Ile Ala Pro Arg Glu Tyr Cys Lys Asp Leu
 675 680 685

Asn Ala Ser Asp Asn Asn Thr Glu Phe Leu Lys Asn Phe Ile Glu Leu
 30 690 695 700

Met Glu Lys Val Thr Pro Asp Ser Lys Gln Cys Asn Asn Phe Leu Leu
 705 710 715 720

35 His Asn Leu Ile Leu Asp Thr Gly Ile Thr Gln Gln Leu Val Glu Arg
 725 730 735

Val Trp Arg Asp Gln Asp Leu Asn Thr Tyr Ser Leu Leu Ala Val Phe
 740 745 750

40 Ala Ala Thr Asp Gly Gly Ile Thr Arg Val Phe Pro Asn Lys Ala Ala
 755 760 765

Glu Asp Trp Thr Glu Asn Pro Glu Pro Phe Asn Ala Ser Phe Tyr Arg
 45 770 775 780

Arg Ser Leu Asp Asn His Gly Tyr Val Phe Lys Pro Pro His Gln Asp
 785 790 795 800

50 Ala Leu Leu Arg Pro Leu Glu Leu Glu Asn Asp Thr Val Gly Ile Leu
 805 810 815

Val Ser Thr Ala Val Glu Leu Ser Leu Gly Arg Arg Thr Leu Arg Pro
 820 825 830

55 Ala Val Val Gly Val Lys Leu Asp Leu Glu Ala Trp Ala Glu Lys Phe
 835 840 845

Lys Val Leu Ala Ser Asn Arg Thr His Gln Asp Gln Pro Gln Lys Cys

	850	855	860
	Gly Pro Asn Ser His Cys Glu Met Asp Cys Glu Val Asn Asn Glu Asp		
865	870	875	880
5	Leu Leu Cys Val Leu Ile Asp Asp Gly Gly Phe Leu Val Leu Ser Asn		
	885	890	895
10	Gln Asn His Gln Trp Asp Gln Val Gly Arg Phe Phe Ser Glu Val Asp		
	900	905	910
	Ala Asn Leu Met Leu Ala Leu Tyr Asn Asn Ser Phe Tyr Thr Arg Lys		
	915	920	925
15	Glu Ser Tyr Asp Tyr Gln Ala Ala Cys Ala Pro Gln Pro Pro Gly Asn		
	930	935	940
	Leu Gly Ala Ala Pro Arg Gly Val Phe Val Pro Thr Val Ala Asp Phe		
	945	950	955
20	Leu Asn Leu Ala Trp Trp Thr Ser Ala Ala Ala Trp Ser Leu Phe Gln		
	965	970	975
	Gln Leu Leu Tyr Gly Leu Ile Tyr His Ser Trp Phe Gln Ala Asp Pro		
25	980	985	990
	Ala Glu Ala Glu Gly Ser Pro Glu Thr Arg Glu Ser Ser Cys Val Met		
	995	1000	1005
30	Lys Gln Thr Gln Tyr Tyr Phe Gly Ser Val Asn Ala Ser Tyr Asn Ala		
	1010	1015	1020
	Ile Ile Asp Cys Gly Asn Cys Ser Arg Leu Phe His Ala Gln Arg Leu		
	1025	1030	1035
35	Thr Asn Thr Asn Leu Leu Phe Val Val Ala Glu Lys Pro Leu Cys Ser		
	1045	1050	1055
	Gln Cys Glu Ala Gly Arg Leu Leu Gln Lys Glu Thr His Cys Pro Ala		
40	1060	1065	1070
	Asp Gly Pro Glu Gln Cys Glu Leu Val Gln Arg Pro Arg Tyr Arg Arg		
	1075	1080	1085
45	Gly Pro His Ile Cys Phe Asp Tyr Asn Ala Thr Glu Asp Thr Ser Asp		
	1090	1095	1100
	Cys Gly Arg Gly Ala Ser Phe Pro Pro Ser Leu Gly Val Leu Val Ser		
	1105	1110	1115
50	Leu Gln Leu Leu Leu Leu Gly Leu Pro Pro Arg Pro Gln Pro Gln		
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<210> 21
<211> 3770

<212> DNA
<213> *Homo sapiens*

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	gggcgcgtcg	gagggagccc	agcatggccg	ggccggggtc	gccgcgcgc	ggtccccggg	180
	gggcctcgcc	gcttctcgct	ccgcgcgttc	tctacgcgc	gctggggac	gtggtcgcct	240
	cgagcagca	gataccgtct	tccgtggta	agctctggc	ctcgctttt	ggtggggaga	300
10	taaaatccat	tgtctgtaag	tactccggtt	cccaagcttc	gcaaaagaaa	tacaaagagt	360
	atgagaaaaga	cgttgccata	gaagaaaattg	atggcctcca	actgttaaag	aagctggcaa	420
	agaacatgga	agagatgttt	cacaagaagt	ctgaggccgt	caggcgtctg	gtggaggctg	480
	cagaagaagc	acacctgaaa	catgaattt	atgcagactt	acagtatgaa	tacttcaatg	540
	ctgtgctgat	aatgaaaagg	gacaaaagacg	ggaattttt	ggagctggga	aaggaattca	600
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	aagtaccaac	gaacatgtac	aacaaagacc	ctgcaattgt	caatggggtt	tattggctcg	720
	aatctctaaa	caaagttttt	gtagataact	ttgaccgtga	cccatctctc	atatggca	780
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	agaatggagt	cattgcctt	gactgcagga	accgaaaatg	gtacatccag	gcagcaactt	900
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	acataattgc	ttataatgag	gagcttca	atgtggaaacc	ttgcctgaat	ggaactttgg	1080
	tgcaagccga	caggacaaac	aaagagcact	tcagggagca	tctggacaaa	ctttcgcca	1140
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	tcacataccct	cattggacga	gaggctgcgt	ttgcagacaa	tctaaagtgg	atggcctgtg	1380
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	tgtgacaaa	tgactactat	tatacagaca	tcaaggggtac	tccttctagt	ttaggtgtgg	1980
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	tgcattactt	agaacatccc	gatgtgttct	tggcagatga	atggctctac	tgcaacactg	2100
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	gcaaagaacc	tctgtccatg	tgtgataaaag	aattgtatca	agaagtcctt	tttgacgcgg	2220
	tggtgagtgc	ccccattgaa	gcgtatttgg	ccagcctggc	cctcaacaaa	tctgaaaattt	2280
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	cagcaagtac	atccatccag	ctccctggat	aacggaaatc	tcctgtggtg	gcagctgtag	2580
	gcattcagat	aaaacttggaa	ttttccaaa	ggaagttctg	gactgtccagc	agacagtgtg	2640
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	gtgagatcga	gggagctgt	atgaacaaaat	tgctaaacaat	gggctccctt	aaaagaattt	2820
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	tcatccagca	aatcccaagc	agcaacactgt	tcatgggttg	ggtggacacgc	agctgcctt	3180
	gtgaatctgt	ggccccatc	accatggcac	ccattgaaat	caggatataat	gaatccctta	3240
	agtgtgaacq	tctaaaggcc	caqaaqatca	qaaggcggccc	agaatcttq	catqcttcc	3300

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 5 **tgtgcgt** ataaaacttt aaagatatgt **tgacaaaaa** ag ttatctatca tcttttact 3600
 ttgccagtca tgcaaatgtg agtttgcac **atgataatca** cccttcatca gaaatgggac 3660
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 tactttttaa ataaaagtata taaaatcat aaaaaaaaaa aaaaaaaaaa 3770

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 <212> PRT
 <213> *Homo sapiens*

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 20 25 30

Ser Glu Gln Gln Ile Pro Leu Ser Val Val Lys Leu Trp Ala Ser Ala
 35 40 45

25 Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln
 50 55 60

Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
 30 65 70 75 80

Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Asn Met Glu
 85 90 95

35 Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
 100 105 110

Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
 115 120 125

40 Glu Tyr Phe Asn Ala Val Leu Ile Asn Glu Arg Asp Lys Asp Gly Asn
 130 135 140

Phe Leu Glu Leu Gly Lys Glu Phe Ile Leu Ala Pro Asn Asp His Phe
 45 145 150 155 160

Asn Asn Leu Pro Val Asn Ile Ser Leu Ser Asp Val Gln Val Pro Thr
 165 170 175

50 Asn Met Tyr Asn Lys Asp Pro Ala Ile Val Asn Gly Val Tyr Trp Ser
 180 185 190

Glu Ser Leu Asn Lys Val Phe Val Asp Asn Phe Asp Arg Asp Pro Ser
 195 200 205

55 Leu Ile Trp Gln Tyr Phe Gly Ser Ala Lys Gly Phe Phe Arg Gln Tyr
 210 215 220

Pro Gly Ile Lys Trp Glu Pro Asp Glu Asn Gly Val Ile Ala Phe Asp

225	230	235	240
Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp			
245	250	255	
5	Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu		
	260	265	270
10	Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp		
	275	280	285
	Asp Asp Phe Phe Asn Ile Ile Ala Tyr Asn Glu Glu Leu His Tyr Val		
	290	295	300
15	Glu Pro Cys Leu Asn Gly Thr Leu Val Gln Ala Asp Arg Thr Asn Lys		
	305	310	315
	Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly		
	325	330	335
20	Met Leu Asp Ile Ala Leu Asn Glu Ala Phe Asn Ile Leu Ser Asp Phe		
	340	345	350
25	Asn His Thr Gly Gln Gly Ser Ile Cys Ser Gln Ala Ile Met Leu Ile		
	355	360	365
	Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn		
	370	375	380
30	Trp Pro Asp Arg Lys Val Arg Ile Phe Thr Tyr Leu Ile Gly Arg Glu		
	385	390	395
	Ala Ala Phe Ala Asp Asn Leu Lys Trp Met Ala Cys Ala Asn Lys Gly		
	405	410	415
35	Phe Phe Thr Gln Ile Ser Thr Leu Ala Asp Val Gln Glu Asn Val Met		
	420	425	430
40	Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His		
	435	440	445
	Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Thr Asp Asp		
	450	455	460
45	Gln Gly Pro Val Leu Met Thr Thr Val Ala Met Pro Val Phe Ser Lys		
	465	470	475
	Gln Asn Glu Thr Arg Ser Lys Gly Ile Leu Leu Gly Val Val Gly Thr		
	485	490	495
50	Asp Val Pro Val Lys Glu Leu Leu Lys Thr Ile Pro Lys Tyr Lys Leu		
	500	505	510
55	Gly Ile His Gly Tyr Ala Phe Ala Ile Thr Asn Asn Gly Tyr Ile Leu		
	515	520	525
	Thr His Pro Glu Leu Arg Leu Leu Tyr Glu Glu Gly Lys Lys Arg Arg		
	530	535	540

Lys Pro Asn Tyr Ser Ser Val Asp Leu Ser Glu Val Glu Trp Glu Asp
 545 550 555 560

Arg Asp Asp Val Leu Arg Asn Ala Met Val Asn Arg Lys Thr Gly Lys
 5 565 570 575

Phe Ser Met Glu Val Lys Lys Thr Val Asp Lys Gly Lys Arg Val Leu
 580 585 590

10 Val Met Thr Asn Asp Tyr Tyr Thr Asp Ile Lys Gly Thr Pro Phe
 595 600 605

Ser Leu Gly Val Ala Leu Ser Arg Gly His Gly Lys Tyr Phe Phe Arg
 610 615 620

15 Gly Asn Val Thr Ile Glu Glu Gly Leu His Asp Leu Glu His Pro Asp
 625 630 635 640

Val Ser Leu Ala Asp Glu Trp Ser Tyr Cys Asn Thr Asp Leu His Pro
 20 645 650 655

Glu His Arg His Leu Ser Gln Leu Glu Ala Ile Lys Leu Tyr Leu Lys
 660 665 670

25 Gly Lys Glu Pro Leu Leu Gln Cys Asp Lys Glu Leu Ile Gln Glu Val
 675 680 685

Leu Phe Asp Ala Val Val Ser Ala Pro Ile Glu Ala Tyr Trp Thr Ser
 690 695 700

30 Leu Ala Leu Asn Lys Ser Glu Asn Ser Asp Lys Gly Val Glu Val Ala
 705 710 715 720

Phe Leu Gly Thr Arg Thr Gly Leu Ser Arg Ile Asn Leu Phe Val Gly
 35 725 730 735

Ala Glu Gln Leu Thr Asn Gln Asp Phe Leu Lys Ala Gly Asp Lys Glu
 740 745 750

40 Asn Ile Phe Asn Ala Asp His Phe Pro Leu Trp Tyr Arg Arg Ala Ala
 755 760 765

Glu Gln Ile Pro Gly Ser Phe Val Tyr Ser Ile Pro Phe Ser Thr Gly
 770 775 780

45 Pro Val Asn Lys Ser Asn Val Val Thr Ala Ser Thr Ser Ile Gln Leu
 785 790 795 800

Leu Asp Glu Arg Lys Ser Pro Val Val Ala Ala Val Gly Ile Gln Met
 50 805 810 815

Lys Leu Glu Phe Phe Gln Arg Lys Phe Trp Thr Ala Ser Arg Gln Cys
 820 825 830

55 Ala Ser Leu Asp Gly Lys Cys Ser Ile Ser Cys Asp Asp Glu Thr Val
 835 840 845

Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe Ile Leu Val Ser Glu Asp
 850 855 860

Tyr Thr Gln Thr Gly Asp Phe Phe Gly Glu Ile Glu Gly Ala Val Met
 865 870 875 880

5 Asn Lys Leu Leu Thr Met Gly Ser Phe Lys Arg Ile Thr Leu Tyr Asp
 885 890 895

Tyr Gln Ala Met Cys Arg Ala Asn Lys Glu Ser Ser Asp Gly Ala His
 900 905 910

10 Gly Leu Leu Asp Pro Tyr Asn Ala Phe Leu Ser Ala Val Lys Trp Ile
 915 920 925

Met Thr Glu Leu Val Leu Phe Leu Val Glu Phe Asn Leu Cys Ser Trp
 15 930 935 940

Trp His Ser Asp Met Thr Ala Lys Ala Gln Lys Leu Lys Gln Thr Leu
 945 950 955 960

20 Glu Pro Cys Asp Thr Glu Tyr Pro Ala Phe Val Ser Glu Arg Thr Ile
 965 970 975

Lys Glu Thr Thr Gly Asn Ile Ala Cys Glu Asp Cys Ser Lys Ser Phe
 980 985 990

25 Val Ile Gln Gln Ile Pro Ser Ser Asn Leu Phe Met Val Val Val Asp
 995 1000 1005

Ser Ser Cys Leu Cys Glu Ser Val Ala Pro Ile Thr Met Ala Pro Ile
 30 1010 1015 1020

Glu Ile Arg Tyr Asn Glu Ser Leu Lys Cys Glu Arg Leu Lys Ala Gln
 1025 1030 1035 1040

35 Lys Ile Arg Arg Arg Pro Glu Ser Cys His Gly Phe His Pro Glu Glu
 1045 1050 1055

Asn Ala Arg Glu Cys Gly Ala Pro Ser Leu Gln Ala Gln Thr Val
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40 Leu Leu Leu Pro Leu Leu Met Leu Phe Ser Arg
 1075 1080 1085

45 <210> 23
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 <213> Homo sapiens

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Arg Thr Ala Arg Pro Trp Pro Gly Cys Gly Pro His Pro Gly Pro Gly
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Thr Arg Arg Pro Thr Ser Gly Pro Pro Arg Pro Leu Trp Leu Leu Leu
 35 40 45

Pro Leu Leu Pro Leu Leu Ala Ala Pro Gly Ala Ser Ala Tyr Ser Phe
 50 55 60

Pro Gln Gln His Thr Met Gln His Trp Ala Arg Arg Leu Glu Gln Glu
 5 65 70 75 80

Val Asp Gly Val Met Arg Ile Phe Gly Gly Val Gln Gln Leu Arg Glu
 85 90 95

10 Ile Tyr Lys Asp Asn Arg Asn Leu Phe Glu Val Gln Glu Asn Glu Pro
 100 105 110

Gln Lys Leu Val Glu Lys Val Ala Gly Asp Ile Glu Ser Leu Leu Asp
 115 120 125

15 Arg Lys Val Gln Ala Leu Lys Arg Leu Ala Asp Ala Ala Glu Asn Phe
 130 135 140

Gln Lys Ala His Arg Trp Gln Asp Asn Ile Lys Glu Glu Asp Ile Val
 20 145 150 155 160

Tyr Tyr Asp Ala Lys Ala Asp Ala Glu Leu Asp Asp Pro Glu Ser Glu
 165 170 175

25 Asp Val Glu Arg Gly Ser Lys Ala Ser Thr Leu Arg Leu Asp Phe Ile
 180 185 190

Glu Asp Pro Asn Phe Lys Asn Lys Val Asn Tyr Ser Tyr Ala Ala Val
 195 200 205

30 Gln Ile Pro Thr Asp Ile Tyr Lys Gly Ser Thr Val Ile Leu Asn Glu
 210 215 220

Leu Asn Trp Thr Glu Ala Leu Glu Asn Val Phe Met Glu Asn Arg Arg
 35 225 230 235 240

Gln Asp Pro Thr Leu Leu Trp Gln Val Phe Gly Ser Ala Thr Gly Val
 245 250 255

40 Thr Arg Tyr Tyr Pro Ala Thr Pro Trp Arg Ala Pro Lys Lys Ile Asp
 260 265 270

Leu Tyr Asp Val Arg Arg Pro Trp Tyr Ile Gln Gly Ala Ser Ser
 275 280 285

45 Pro Lys Asp Met Val Ile Ile Val Asp Val Ser Gly Ser Val Ser Gly
 290 295 300

Leu Thr Leu Lys Leu Met Lys Thr Ser Val Cys Glu Met Leu Asp Thr
 50 305 310 315 320

Leu Ser Asp Asp Asp Tyr Val Asn Val Ala Ser Phe Asn Glu Lys Ala
 325 330 335

55 Gln Pro Val Ser Cys Phe Thr His Leu Val Gln Ala Asn Val Arg Asn
 340 345 350

Lys Lys Val Phe Lys Glu Ala Val Gln Gly Met Val Ala Lys Gly Thr
 355 360 365

Thr Gly Tyr Lys Ala Gly Phe Glu Tyr Ala Phe Asp Gln Leu Gln Asn
 370 375 380
 5 Ser Asn Ile Thr Arg Ala Asn Cys Asn Lys Met Ile Met Met Phe Thr
 385 390 395 400
 Asp Gly Gly Glu Asp Arg Val Gln Asp Val Phe Glu Lys Tyr Asn Trp
 405 410 415
 10 Pro Asn Arg Thr Val Arg Val Phe Thr Phe Ser Val Gly Gln His Asn
 420 425 430
 Tyr Asp Val Thr Pro Leu Gln Trp Met Ala Cys Ala Asn Lys Gly Tyr
 15 435 440 445
 Tyr Phe Glu Ile Pro Ser Ile Gly Ala Ile Arg Ile Asn Thr Gln Glu
 450 455 460
 20 Tyr Leu Asp Val Leu Gly Arg Pro Met Val Leu Ala Gly Lys Glu Ala
 465 470 475 480
 Lys Gln Val Gln Trp Thr Asn Val Tyr Glu Asp Ala Leu Gly Leu Gly
 485 490 495
 25 Leu Val Val Thr Gly Thr Leu Pro Val Phe Asn Leu Thr Gln Asp Gly
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 Pro Gly Glu Lys Lys Asn Gln Leu Ile Leu Gly Val Met Gly Ile Asp
 30 515 520 525
 Val Ala Leu Asn Asp Ile Lys Arg Leu Thr Pro Asn Tyr Thr Leu Gly
 530 535 540
 35 Ala Asn Gly Tyr Val Phe Ala Ile Asp Leu Asn Gly Tyr Val Leu Leu
 545 550 555 560
 His Pro Asn Leu Lys Pro Gln Thr Thr Asn Phe Arg Glu Pro Val Thr
 565 570 575
 40 Leu Asp Phe Leu Asp Ala Glu Leu Glu Asp Glu Asn Lys Glu Glu Ile
 580 585 590
 Arg Arg Ser Met Ile Asp Gly Asn Lys Gly His Lys Gln Ile Arg Thr
 45 595 600 605
 Leu Val Lys Ser Leu Asp Glu Arg Tyr Ile Asp Glu Val Thr Arg Asn
 610 615 620
 50 Tyr Thr Trp Val Pro Ile Arg Ser Thr Asn Tyr Ser Leu Gly Leu Val
 625 630 635 640
 Leu Pro Pro Tyr Ser Thr Phe Tyr Leu Gln Ala Asn Leu Ser Asp Gln
 645 650 655
 55 Ile Leu Gln Val Lys Tyr Phe Glu Phe Leu Leu Pro Ser Ser Phe Glu
 660 665 670
 Ser Glu Gly His Val Phe Ile Ala Pro Arg Glu Tyr Cys Lys Asp Leu

	675	680	685
	Asn Ala Ser Asp Asn Asn Thr Glu Phe Leu Lys Asn Phe Ile Glu Leu		
	690	695	700
5	Met Glu Lys Val Thr Pro Asp Ser Lys Gln Cys Asn Asn Phe Leu Leu		
	705	710	715
	His Asn Leu Ile Leu Asp Thr Gly Ile Thr Gln Gln Leu Val Glu Arg		
10	725	730	735
	Val Trp Arg Asp Gln Asp Leu Asn Thr Tyr Ser Leu Leu Ala Val Phe		
	740	745	750
15	Ala Ala Thr Asp Gly Gly Ile Thr Arg Val Phe Pro Asn Lys Ala Ala		
	755	760	765
	Glu Asp Trp Thr Glu Asn Pro Glu Pro Phe Asn Ala Ser Phe Tyr Arg		
	770	775	780
20	Arg Ser Leu Asp Asn His Gly Tyr Val Phe Lys Pro Pro His Gln Asp		
	785	790	795
	Ala Leu Leu Arg Pro Leu Glu Leu Glu Asn Asp Thr Val Gly Ile Leu		
25	805	810	815
	Val Ser Thr Ala Val Glu Leu Ser Leu Gly Arg Arg Thr Leu Arg Pro		
	820	825	830
30	Ala Val Val Gly Val Lys Leu Asp Leu Glu Ala Trp Ala Glu Lys Phe		
	835	840	845
	Lys Val Leu Ala Ser Asn Arg Thr His Gln Asp Gln Pro Gln Lys Cys		
	850	855	860
35	Gly Pro Asn Ser His Cys Glu Met Asp Cys Glu Val Asn Asn Glu Asp		
	865	870	875
	Leu Leu Cys Val Leu Ile Asp Asp Gly Gly Phe Leu Val Leu Ser Asn		
40	885	890	895
	Gln Asn His Gln Trp Asp Gln Val Gly Arg Phe Phe Ser Glu Val Asp		
	900	905	910
45	Ala Asn Leu Met Leu Ala Leu Tyr Asn Asn Ser Phe Tyr Thr Arg Lys		
	915	920	925
	Glu Ser Tyr Asp Tyr Gln Ala Ala Cys Ala Pro Gln Pro Pro Gly Asn		
	930	935	940
50	Leu Gly Ala Ala Pro Arg Gly Val Phe Val Pro Thr Val Ala Asp Phe		
	945	950	955
	Leu Asn Leu Ala Trp Trp Thr Ser Ala Ala Ala Trp Ser Leu Phe Gln		
55	965	970	975
	Gln Leu Leu Tyr Gly Leu Ile Tyr His Ser Trp Phe Gln Ala Asp Pro		
	980	985	990

Ala Glu Ala Glu Gly Ser Pro Glu Thr Arg Glu Ser Ser Cys Val Met
 995 1000 1005

Lys Gln Thr Gln Tyr Tyr Phe Gly Ser Val Asn Ala Ser Tyr Asn Ala
 5 1010 1015 1020

Ile Ile Asp Cys Gly Asn Cys Ser Arg Leu Phe His Ala Gln Arg Leu
 1025 1030 1035 1040

10 Thr Asn Thr Asn Leu Leu Phe Val Val Ala Glu Lys Pro Leu Cys Ser
 1045 1050 1055

Gln Cys Glu Ala Gly Arg Leu Leu Gln Lys Glu Thr His Cys Pro Ala
 1060 1065 1070

15 Asp Gly Pro Glu Gln Cys Glu Leu Val Gln Arg Pro Arg Tyr Arg Arg
 1075 1080 1085

Gly Pro His Ile Cys Phe Asp Tyr Asn Ala Thr Glu Asp Thr Ser Asp
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Cys Gly Arg Gly Ala His His His His His His
 1105 1110 1115

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40 Phe Gly Gly Glu Ile Lys Ser Ile Ala Ala Lys Tyr Ser Gly Ser Gln
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Leu Leu Gln Lys Lys Tyr Lys Glu Tyr Glu Lys Asp Val Ala Ile Glu
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Glu Ile Asp Gly Leu Gln Leu Val Lys Lys Leu Ala Lys Ile Met Glu
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50 Glu Met Phe His Lys Lys Ser Glu Ala Val Arg Arg Leu Val Glu Ala
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Ala Glu Glu Ala His Leu Lys His Glu Phe Asp Ala Asp Leu Gln Tyr
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Cys Arg Asn Arg Lys Trp Tyr Ile Gln Ala Ala Thr Ser Pro Lys Asp			
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20	Val Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu Arg Leu		
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25	Thr Ile Ala Lys Gln Thr Val Ser Ser Ile Leu Asp Thr Leu Gly Asp		
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Asp Asp Phe Phe Asn Ile Ile Thr Tyr Asn Glu Glu Leu His Tyr Val			
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Glu His Phe Arg Glu His Leu Asp Lys Leu Phe Ala Lys Gly Ile Gly			
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Thr Asp Gly Ala Val Asp Thr Tyr Asp Thr Ile Phe Ala Lys Tyr Asn			
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	400		
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Glu Tyr Leu His Val Leu Ser Arg Pro Lys Val Ile Asp Gln Glu His			
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Asp Val Val Trp Thr Glu Ala Tyr Ile Asp Ser Thr Leu Pro Gln Ala			
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10 Ile Pro Lys Tyr Lys Leu Gly Ile His Gly Tyr Ala Phe Ala Ile Thr
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Cys Asp Asp Glu Thr Val Asn Cys Tyr Leu Ile Asp Asn Asn Gly Phe
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20 Val Glu Gly Ala Val Met Asn Lys Leu Leu Thr Met Gly Ser Phe Lys
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Ser Ala Ala Lys Trp Ile Met Thr Glu Leu Val Leu Phe Leu Val Glu
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Phe Asn Leu Cys Ser Trp Trp His Ser Asp Met Thr Ala Lys Ala Gln
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caagaaaaacc cagaaacata tgaggacagc ttctataaaaa gaatctaga taacgataac 2280
tatgttttca ctgctccctt ctttaacaaa agtggactgt tgctttaga atcaggcatc 2340
atggtaagca aagctgtaga aatatacatc caagggaaaac ttcttaaacc tgcaatgtt 2400
50 ggaattaaaa ttgatgtaaa ttctggata gagaatttca cccaaacatc aatcaggat 2460
ccgtgtctg gtccagttt gatgtttaaa agaaacagt atgtatggg ttgtgtgatt 2520
ctagatgtatg gtgggtttct ttgtatggca aatcatgtatg attatactaa ccagattgaa 2580
agtttttttgg gagagattga cccaaatgg atgagacacc tggttaatatt atcagtttat 2640
gcttttaaca aatcttacga ttatcgtca gtgtgtgagc ctggctgc accaaaacaa 2700
55 ggagcaggac atcgctcagc atatgtgcca tcaatagcag acatcttaca cattggctgg 2760
tggccactg cagctgcattt gtcattttca cagcagttt tctttagtgc gacctttcca 2820
cgacttctt aagcagttga gatggaaatg gatgacttta ccgcctctt gtcggacgg 2880
atgtgcattt ctgaacaaaac ccagtttttca ttgtataatg atgacaaatc cttcagttt 2940
gtcttggact gtggtaactg ttccaaatc ttacatgtt aaaaacttat gaacaccaac 3000

ttaatattca taatggttga gagcaaaggg acttgtcctt gtgacacacag attgctcata 3060
caagctgagc agacttctga cgggtccagat ccttggata tggttaagtg a 3111

gtcttggact gtggtaactg ttccagaatc tttcacgtt aaaaacttat gaacaccaac 3000
 ttaatattca taatggttga gagcaaaggc acttgcctt gtgacacaeg attgctcata 3060
 caagctgagc agacttctga cggtccagat cttgtgata tggtaagca acccagatac 3120
 cgaaaaggc ctgatgtctg ttttataac aatgccttgg aggattatac cgactgtggt 3180
 5 ggttttttttga 3192

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 <211> 1091
 10 <212> PRT
 <213> Sus scrofa

<400> 33
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Leu Leu Ile Gly Pro Ser Ser Gln Glu Pro Phe Pro Ser Ala Val Thr
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20 Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
 35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
 50 55 60

25 Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
 30 85 90 95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
 100 105 110

35 Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
 115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
 130 135 140

40 Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
 145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
 45 165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
 180 185 190

50 Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
 195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
 210 215 220

55 Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
 225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile

	245	250	255
	Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile		
	260	265	270
5	Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe		
	275	280	285
	Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe		
10	290	295	300
	Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp		
	305	310	315
			320
15	Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly		
	325	330	335
	Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala		
	340	345	350
20	Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg		
	355	360	365
	Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val		
25	370	375	380
	Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln		
	385	390	395
			400
30	Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile		
	405	410	415
	Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg		
	420	425	430
35	Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn		
	435	440	445
	Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu		
40	450	455	460
	Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys		
	465	470	475
			480
45	Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp		
	485	490	495
	Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr		
	500	505	510
50	Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln		
	515	520	525
	Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp		
55	530	535	540
	Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile		
	545	550	555
			560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
 565 570 575

5 Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
 580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
 595 600 605

10 Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
 610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
 625 630 635 640

15 Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
 645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
 20 660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
 675 680 685

25 Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
 690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
 705 710 715 720

30 Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
 725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
 35 740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
 755 760 765

40 Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
 770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
 785 790 795 800

45 Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
 805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
 50 820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
 835 840 845

55 Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
 850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
 865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
 885 890 895

5 Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
 900 905 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
 915 920 925

10 Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
 930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
 15 945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
 965 970 975

20 Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
 980 985 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
 995 1000 1005

25 Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
 1010 1015 1020

Thr Ser Asp Gly Pro Asp Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
 30 1025 1030 1035 1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Ala Leu Glu Asp Tyr
 1045 1050 1055

35 Thr Asp Cys Gly Gly Val Ser Gly Leu Asn Pro Ser Leu Trp Ser Ile
 1060 1065 1070

Phe Gly Ile Gln Cys Val Leu Leu Trp Leu Leu Ser Gly Ser Arg His
 1075 1080 1085

40 Tyr Gln Leu
 1090

45 <210> 34
 <211> 1018
 <212> PRT
 <213> Sus scrofa

50 <400> 34
 Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
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Leu Leu Ile Gly Pro Ser Ser Gln Glu Pro Phe Pro Ser Ala Val Thr
 55 20 25 30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
 35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
 50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 5 65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
 85 90 95

10 Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
 100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
 115 120 125

15 Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
 130 135 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
 20 145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
 165 170 175

25 Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
 180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
 195 200 205

30 Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
 210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
 35 225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
 245 250 255

40 Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
 260 265 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
 275 280 285

45 Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
 290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
 50 305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
 325 330 335

55 Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
 340 345 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
 355 360 365

Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
 370 375 380

5 Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
 385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Glu Ile Pro Ser Ile
 405 410 415

10 Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
 420 425 430

15 Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
 435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
 450 455 460

20 Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
 465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
 485 490 495

25 Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
 500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
 515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
 530 535 540

35 Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
 545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
 565 570 575

40 Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
 580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
 595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
 610 615 620

50 Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
 625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
 645 650 655

55 Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
 660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp

	675	680	685
	Leu Ile Asn Arg Val Leu	Leu Asp Ala Gly Phe Thr	Asn Glu Leu Val
	690	695	700
5	Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg		
	705	710	715
	Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala		
10	725	730	735
	Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr		
	740	745	750
15	Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe		
	755	760	765
	Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys		
	770	775	780
20	Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val		
	785	790	795
	Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr		
25	805	810	815
	Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn		
	820	825	830
30	Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu		
	835	840	845
	Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly		
	850	855	860
35	Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr		
	865	870	875
	Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala		
40	885	890	895
	Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile		
	900	905	910
45	Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Trp Ser		
	915	920	925
	Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu		
	930	935	940
50	Ala Val Glu Met Glu Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln		
	945	950	955
	Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys		
55	965	970	975
	Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His		
	980	985	990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
 995 1000 1005

 Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu
 5 1010 1015

 10 <210> 35
 <211> 1036
 <212> PRT
 <213> Sus scrofa

 <400> 35
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 Leu Leu Ile Gly Pro Ser Ser Gln Glu Pro Phe Pro Ser Ala Val Thr
 20 25 30

 20 Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
 35 40 45

 Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
 50 55 60

 25 Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 65 70 75 80

 Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
 30 85 90 95

 Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
 100 105 110

 35 Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
 115 120 125

 Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
 130 135 140

 40 Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
 145 150 155 160

 Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
 45 165 170 175

 Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
 180 185 190

 50 Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
 195 200 205

 Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
 210 215 220

 55 Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
 225 230 235 240

 Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile

	245	250	255
	Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile		
	260	265	270
5	Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe		
	275	280	285
10	Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe		
	290	295	300
	Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp		
	305	310	315
15	Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly		
	325	330	335
	Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala		
	340	345	350
20	Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg		
	355	360	365
25	Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val		
	370	375	380
	Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln		
	385	390	395
30	Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile		
	405	410	415
	Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg		
	420	425	430
35	Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn		
	435	440	445
	Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu		
40	450	455	460
	Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys		
	465	470	475
45	Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp		
	485	490	495
	Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr		
	500	505	510
50	Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln		
	515	520	525
	Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp		
55	530	535	540
	Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile		
	545	550	555
			560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
 565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
 5 580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
 595 600 605

10 Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
 610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
 625 630 635 640

15 Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
 645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
 20 660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
 675 680 685

25 Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
 690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
 705 710 715 720

30 Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
 725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
 35 740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
 755 760 765

40 Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
 770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
 785 790 795 800

45 Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
 805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
 50 820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
 835 840 845

55 Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
 850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
 865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
 885 890 895

5 Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
 900 905 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Trp Ser
 915 920 925

10 Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
 930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
 15 945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
 965 970 975

20 Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
 980 985 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
 995 1000 1005

25 Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
 1010 1015 1020

Thr Ser Asp Gly Pro Asp Pro Cys Asp Met Val Lys
 30 1025 1030 1035

<210> 36
 <211> 1063
 35 <212> PRT
 <213> Sus scrofa

<400> 36
 Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
 40 1 5 10 15

Leu Leu Ile Gly Pro Ser Ser Gln Glu Pro Phe Pro Ser Ala Val Thr
 20 25 30

45 Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
 35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
 50 55 60

50 Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
 55 85 90 95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
 100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
 115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
 5 130 135 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
 145 150 155 160

10 Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
 165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
 180 185 190

15 Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
 195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
 20 210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
 225 230 235 240

25 Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
 245 250 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
 260 265 270

30 Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
 275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
 35 290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
 305 310 315 320

40 Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
 325 330 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
 340 345 350

45 Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
 355 360 365

Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
 50 370 375 380

Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
 385 390 395 400

55 Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
 405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
 420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
 435 440 445

5 Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
 450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
 465 470 475 480

10 Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
 485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
 15 500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
 515 520 525

20 Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
 530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
 545 550 555 560

25 Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
 565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
 30 580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
 595 600 605

35 Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
 610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
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Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
 675 680 685

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Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
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55 Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
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Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr

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	Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr			
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	Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu			
	835	840	845	
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	Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr			
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	Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys			
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	Thr Ser Asp Gly Pro Asp Pro Cys Asp Met Val Lys Gln Pro Arg Tyr			
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30 Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
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Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
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40 Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
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Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
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Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
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	Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly			
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	Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg			
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20	Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val			
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	Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln			
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	Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile			
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 675 680 685

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	gccttggtat	taccaaccta	cagttttac	tatataaaa	ccaaactaga	agagacaata	1860
	actcaggcca	gataaaaaaa	gggcaaaatg	aaggattcg	aaaccctgaa	gccagataat	1920
	tttgaagaat	ctggctatac	attcatagca	ccaagagatt	actgcaatga	cctgaaaata	1980
25	tcggataata	acactgaatt	tctttaaat	ttcaacgagt	ttattgtatag	aaaaactcca	2040
	aacaacccat	catgtaacgc	ggatttgatt	aatagagtct	tgcttgatgc	aggctttaca	2100
	aatgaacttg	tccaaaatta	ctggagtaag	cagaaaaata	tcaagggagt	gaaagcaca	2160
30	tttgttgtga	ctgatgttgg	gattaccaga	gtttatccca	aagaggctgg	agaaaatttg	2220
	caagaaaaacc	cagagacata	tgaggacagc	ttctataaaa	ggagccctaga	taatgataac	2280
	tatgttttca	ctgttcccta	ctttaacaaa	agtggacctg	gtgcctatga	atcgggcatt	2340
	atggtaagca	aagctgtaga	aatataatatt	caagggaaac	ttcttaaacc	tgcagttgtt	2400
	ggaattaaaa	ttgatgtaaa	ttcctggata	gagaatttca	ccaaacac	aatcagagat	2460
35	cctgtgtctg	gtccagttt	tgactgtcaaa	agaaaacagt	acgtaatgg	ttgtgtgatt	2520
	ctggatgtat	gtgggtttct	tctgtatggca	aatcatgtat	attatactaa	tcatgttgg	2580
	agattttttgc	gagagattga	tcccagctt	atgagacacc	tggtaatatt	atcagtttat	2640
	gcttttaaca	aatcttata	ttatcgtat	gtatgtgac	cgggtgtc	acccaaaacaa	2700
	ggagcaggac	atcgtctc	atatgtgcca	tcatgtac	acatattaca	aatttggctgg	2760
	tgggccactg	ctgctgcetg	gtctattcta	cagcagttt	tctttagttt	gacctttcca	2820
	cgacttccttgc	aggcagttga	gatggaggat	gtgacttca	cggctccct	gtccaagcag	2880
	agctgcatttgc	ctgaacaaaac	ccagttt	ttcgataa	acagtaaattc	attcagtgt	2940
	gtatttagact	gtggaaactg	ttccagaatc	tttcatggag	aaaagctt	gaacaccaac	3000
	ttaatattca	taatgggtga	gagcaaaagg	acatgtccat	gtgacacac	actgctata	3060
	caagcggagc	agacttctga	cggtccaaat	ccttgtgaca	tggtaagca	acctagat	3120
	cgaaaaaggc	ctgatgtctg	ctttgataac	aatgtcttgg	aggattatac	tgactgtgt	3180
	qgtgtttctg						3190

40 <210> 41
<211> 1018
<212> PRT
<213> *Homo sapiens*

45 <400> 41
Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
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50 Leu Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe Pro Ser Ala Val Thr
 20 25 30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
35 40 45

55 Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
 85 90 95

5 Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
 100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
 115 120 125

10 Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
 130 135 140

Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
 15 145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
 165 170 175

20 Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
 180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
 195 200 205

25 Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
 210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
 30 225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
 245 250 255

35 Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
 260 265 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
 40 275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
 290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
 45 305 310 315 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
 325 330 335

50 Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
 340 345 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
 355 360 365

55 Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
 370 375 380

Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln

385	390	395	400
Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile			
405	410	415	
5	Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg	420	430
425		430	
10	Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn	435	445
440		445	
15	Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu	450	460
455		460	
20	465 Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys	470	480
475		480	
25	Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp	485	495
490		495	
30	500 Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr	505	510
510		510	
35	515 Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln	520	525
525		525	
40	530 Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp	535	540
540		540	
45	545 Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile	550	560
555		560	
50	565 Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln	570	575
575		575	
55	580 Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro	585	590
590		590	
60	595 Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser	600	605
605		605	
65	610 Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg	615	620
620		620	
70	625 Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn	630	640
635		640	
75	645 Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn	650	655
655		655	
80	660 Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn	665	670
670		670	
85	675 Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp	680	685
685		685	
90	690 Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val	695	700
700		700	

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
 705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
 5 725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
 740 745 750

10 Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
 755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
 770 775 780

15 Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
 785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
 20 805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
 820 825 830

25 Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
 835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
 850 855 860

30 Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
 865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
 35 885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val
 900 905 910

40 Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
 915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
 930 935 940

45 Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
 945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
 50 965 970 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
 980 985 990

55 Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
 995 1000 1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu
 1010 1015

5 <210> 42
 <211> 1036
 <212> PRT
 <213> Homo sapiens

10 <400> 42
 Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
 1 5 10 15

15 Leu Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe Pro Ser Ala Val Thr
 20 25 30

20 Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
 35 40 45

25 Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
 50 55 60

30 Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 65 70 75 80

35 Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
 85 90 95

40 Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
 100 105 110

45 Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
 115 120 125

50 Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
 130 135 140

55 Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
 145 150 155 160

60 Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
 165 170 175

65 Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
 180 185 190

70 Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
 195 200 205

75 Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
 210 215 220

80 Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
 225 230 235 240

85 Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
 245 250 255

90 Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
 260 265 270

Arg Thr Ser Val Ser Glu **Met** Leu Glu Thr Leu Ser Asp Asp Asp Phe
 275 280 285
 Val Asn Val Ala Ser Phe **Asn** Ser Asn Ala Gln Asp Val Ser Cys Phe
 5 290 295 300
 Gln His Leu Val Gln Ala **Asn** Val Arg Asn Lys Lys Val Leu Lys Asp
 305 310 315 320
 10 Ala Val Asn Asn Ile Thr **Ala** Lys Gly Ile Thr Asp Tyr Lys Lys Gly
 325 330 335
 Phe Ser Phe Ala Phe Glu **Gln** Leu Leu Asn Tyr Asn Val Ser Arg Ala
 340 345 350
 15 Asn Cys Asn Lys Ile Ile **Met** Leu Phe Thr Asp Gly Gly Glu Glu Arg
 355 360 365
 Ala Gln Glu Ile Phe Asn **Lys** Tyr Asn Lys Asp Lys Lys Val Arg Val
 20 370 375 380
 Phe Arg Phe Ser Val Gly **Gln** His Asn Tyr Glu Arg Gly Pro Ile Gln
 385 390 395 400
 25 Trp Met Ala Cys Glu Asn **Lys** Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
 405 410 415
 Gly Ala Ile Arg Ile Asn **Thr** Gln Glu Tyr Leu Asp Val Leu Gly Arg
 420 425 430
 30 Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
 435 440 445
 Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
 35 450 455 460
 Pro Val Phe Asn Ile Thr **Gly** Gln Phe Glu Asn Lys Thr Asn Leu Lys
 465 470 475 480
 40 Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
 485 490 495
 Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
 500 505 510
 45 Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
 515 520 525
 Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
 530 535 540
 Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
 545 550 555 560
 55 Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
 565 570 575
 Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
 580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
 595 600 605

5 Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg
 610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
 625 630 635 640

10 Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
 645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
 15 660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
 675 680 685

20 Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
 690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
 705 710 715 720

25 Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
 725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
 30 740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
 755 760 765

35 Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
 770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
 785 790 795 800

40 Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
 805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
 45 820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
 835 840 845

50 Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
 850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
 865 870 875 880

55 Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
 885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val

	900	905	910
	Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser		
	915	920	925
5	Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu		
	930	935	940
10	Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln		
	945	950	955
	Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys		
	965	970	975
15	Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His		
	980	985	990
	Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser		
	995	1000	1005
20	Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln		
	1010	1015	1020
	Thr Ser Asp Gly Pro Asn Pro Cys Asp Met Val Lys		
25	1025	1030	1035
	<210> 43		
	<211> 1063		
30	<212> PRT		
	<213> Homo sapiens		
	<400> 43		
	Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser		
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	Leu Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe Pro Ser Ala Val Thr		
	20	25	30
40	Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala		
	35	40	45
	Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr		
	50	55	60
45	Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu		
	65	70	75
	60		
	Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala		
50	85	90	95
	Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln		
	100	105	110
55	Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys		
	115	120	125
	Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg		
	130	135	140

Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
 145 150 155 160

5 Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
 165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
 180 185 190

10 Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
 195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
 15 210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
 225 230 235 240

20 Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
 245 250 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
 260 265 270

25 Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
 275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
 30 290 295 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
 305 310 315 320

35 Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
 325 330 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asp Val Ser Arg Ala
 340 345 350

40 Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Arg
 355 360 365

Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
 45 370 375 380

Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
 385 390 395 400

50 Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
 405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
 420 425 430

55 Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
 435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu

	450	455	460
	Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys		
465	470	475	480
5	Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp		
	485	490	495
10	Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr		
	500	505	510
	Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln		
	515	520	525
15	Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp		
	530	535	540
	Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile		
545	550	555	560
20	Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln		
	565	570	575
	Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro		
25	580	585	590
	Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser		
	595	600	605
30	Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg		
	610	615	620
	Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn		
625	630	635	640
35	Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn		
	645	650	655
	Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn		
40	660	665	670
	Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp		
	675	680	685
45	Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val		
	690	695	700
	Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg		
705	710	715	720
50	Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala		
	725	730	735
	Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr		
55	740	745	750
	Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe		
	755	760	765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
 770 775 780

5 Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
 785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
 805 810 815

10 Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
 820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
 835 840 845

15 Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
 850 855 860

20 Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
 865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
 885 890 895

25 Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val
 900 905 910

Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Trp Ser
 915 920 925

30 Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
 930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
 945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
 965 970 975

40 Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
 980 985 990

Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
 995 1000 1005

45 Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
 1010 1015 1020

Thr Ser Asp Gly Pro Asn Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
 50 1025 1030 1035 1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Val Leu Glu Asp Tyr
 1045 1050 1055

55 Thr Asp Cys Gly Gly Val Ser
 1060

<211> 1091
 <212> PRT
 <213> Homo sapiens

5 <400> 44
 Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
 1 5 10 15
 Leu Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe Pro Ser Ala Val Thr
 10 20 25 30
 Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
 35 40 45
 15 Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
 50 55 60
 Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 65 70 75 80
 20 Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
 85 90 95
 Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
 25 100 105 110
 Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
 115 120 125
 30 Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
 130 135 140
 Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
 145 150 155 160
 35 Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
 165 170 175
 Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
 40 180 185 190
 Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
 195 200 205
 45 Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
 210 215 220
 Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
 225 230 235 240
 50 Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
 245 250 255
 Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
 55 260 265 270
 Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
 275 280 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
 290 295 300
 Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
 5 305 310 315 320
 Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
 325 330 335
 10 Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
 340 345 350
 Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
 355 360 365
 15 Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
 370 375 380
 Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
 20 385 390 395 400
 Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
 405 410 415
 25 Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
 420 425 430
 Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
 435 440 445
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Ser Leu Leu Leu Gln Lys Lys Tyr Lys Asp Val Glu Ser Ser Leu Lys
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10 Ile Glu Glu Val Asp Gly Leu Glu Leu Val Arg Lys Phe Ser Glu Asp
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Met Glu Asn Met Leu Arg Arg Lys Val Glu Ala Val Gln Asn Leu Val
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Glu Ala Ala Glu Glu Ala Asp Leu Asn His Glu Phe Asn Glu Ser Leu
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20 Val Phe Asp Tyr Tyr Asn Ser Val Leu Ile Asn Glu Arg Asp Glu Lys
 145 150 155 160

Gly Asn Phe Val Glu Leu Gly Ala Glu Phe Leu Leu Glu Ser Asn Ala
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25 His Phe Ser Asn Leu Pro Val Asn Thr Ser Ile Ser Ser Val Gln Leu
 180 185 190

Pro Thr Asn Val Tyr Asn Lys Asp Pro Asp Ile Leu Asn Gly Val Tyr
 30 195 200 205

Met Ser Glu Ala Leu Asn Ala Val Phe Val Glu Asn Phe Gln Arg Asp
 210 215 220

35 Pro Thr Leu Thr Trp Gln Tyr Phe Gly Ser Ala Thr Gly Phe Phe Arg
 225 230 235 240

Ile Tyr Pro Gly Ile Lys Trp Thr Pro Asp Glu Asn Gly Val Ile Thr
 245 250 255

40 Phe Asp Cys Arg Asn Arg Gly Trp Tyr Ile Gln Ala Ala Thr Ser Pro
 260 265 270

Lys Asp Ile Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu
 45 275 280 285

Arg Met Thr Ile Ala Lys His Thr Ile Thr Thr Ile Leu Asp Thr Leu
 290 295 300

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 305 310 315 320

Tyr Ile Glu Pro Cys Phe Lys Gly Ile Leu Val Gln Ala Asp Arg Asp
 325 330 335

55 Asn Arg Glu His Phe Lys Leu Leu Val Glu Glu Leu Met Val Lys Gly
 340 345 350

Val Gly Val Val Asp Gln Ala Leu Arg Glu Ala Phe Gln Ile Leu Lys

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	Tyr Asn Trp Pro Asp Cys Lys Val Arg Val Phe Thr Tyr Leu Ile Gly		
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	Arg Glu Val Ser Phe Ala Asp Arg Met Lys Trp Ile Ala Cys Asn Asn		
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	Ser Ser Gln Ala Gln Ser Leu Thr Leu Leu Thr Thr Val Ala Met Pro		
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	Val Phe Ser Lys Lys Asn Glu Thr Arg Ser His Gly Ile Leu Leu Gly		
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	Arg Tyr Lys Leu Gly Val His Gly Tyr Ala Phe Leu Asn Thr Asn Asn		
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	545	550	555
	Lys Lys Leu Lys Pro Lys Pro Asn Tyr Asn Ser Val Asp Leu Ser Glu		
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	Val Glu Trp Glu Asp Gln Ala Glu Ser Leu Arg Thr Ala Met Ile Asn		
	580	585	590
45	Arg Glu Thr Gly Thr Leu Ser Met Asp Val Lys Val Pro Met Asp Lys		
	595	600	605
	Gly Lys Arg Val Leu Phe Leu Thr Asn Asp Tyr Phe Phe Thr Asp Ile		
	610	615	620
50	Ser Asp Thr Pro Phe Ser Leu Gly Val Val Leu Ser Arg Gly His Gly		
	625	630	635
	Glu Tyr Ile Leu Leu Gly Asn Thr Ser Val Glu Glu Gly Leu His Asp		
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	Leu Leu His Pro Asp Leu Ala Leu Ala Gly Asp Trp Ile Tyr Cys Ile		
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 Ile Arg Phe Leu Thr Arg Lys Asp Pro Asp Leu Glu Cys Asp Glu Glu
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Asp Thr Phe Gly Gly Asp Leu Tyr Asn Thr Val Thr Lys Tyr Ser Gly
 65 70 75 80

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Ile Glu Glu Val Asp Gly Leu Glu Leu Val Arg Lys Phe Ser Glu Asp
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Met Glu Asn Met Leu Arg Arg Lys Val Glu Ala Val Gln Asn Leu Val
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 130 135 140

Val Phe Asp Tyr Tyr Asn Ser Val Leu Ile Asn Glu Arg Asp Glu Lys
 145 150 155 160

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 165 170 175

His Phe Ser Asn Leu Pro Val Asn Thr Ser Ile Ser Ser Val Gln Leu
 55 180 185 190

Pro Thr Asn Val Tyr Asn Lys Asp Pro Asp Ile Leu Asn Gly Val Tyr
 195 200 205

Met Ser Glu Ala Leu Asn Ala Val Phe Val Glu Asn Phe Gln Arg Asp
 210 215 220

Pro Thr Leu Thr Trp Gln Tyr Phe Gly Ser Ala Thr Gly Phe Phe Arg
 5 225 230 235 240

Ile Tyr Pro Gly Ile Lys Trp Thr Pro Asp Glu Asn Gly Val Ile Thr
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10 Phe Asp Cys Arg Asn Arg Gly Trp Tyr Ile Gln Ala Ala Thr Ser Pro
 260 265 270

Lys Asp Ile Val Ile Leu Val Asp Val Ser Gly Ser Met Lys Gly Leu
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Gly Glu Asn Asp Phe Val Asn Ile Ile Ala Tyr Asn Asp Tyr Val His
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Tyr Ile Glu Pro Cys Phe Lys Gly Ile Leu Val Gln Ala Asp Arg Asp
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 340 345 350

Val Gly Val Val Asp Gln Ala Leu Arg Glu Ala Phe Gln Ile Leu Lys
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Leu Ile Ser Asp Gly Ala Val Glu Asp Tyr Glu Pro Val Phe Glu Lys
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Tyr Asn Trp Pro Asp Cys Lys Val Arg Val Phe Thr Tyr Leu Ile Gly
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Lys Gly Tyr Tyr Thr Gln Ile Ser Thr Leu Ala Asp Thr Gln Glu Asn
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Asp His Asp Ile Ile Trp Thr Glu Ala Tyr Met Asp Ser Lys Leu Leu
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5 Gly Tyr Ile Leu Ser His Pro Asp Leu Arg Pro Leu Tyr Arg Glu Gly
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Lys Lys Leu Lys Pro Lys Pro Asn Tyr Asn Ser Val Asp Leu Ser Glu
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Arg Glu Thr Gly Thr Leu Ser Met Asp Val Lys Val Pro Met Asp Lys
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Thr Asp Ile Asp Pro Asp His Arg Lys Leu Ser Gln Leu Glu Ala Met
 30 675 680 685

Ile Arg Phe Leu Thr Arg Lys Asp Pro Asp Leu Glu Cys Asp Glu Glu
 690 695 700

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 740 745 750

Ser Leu Phe Val Gly Ser Glu Lys Val Ser Asp Arg Lys Phe Leu Thr
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Pro Glu Asp Glu Ala Ser Val Phe Thr Leu Asp Arg Phe Pro Leu Trp
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Arg Trp Ala Glu Gly Pro Glu Ser Ala Gly Glu Pro Met Val Val Thr
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 820 825 830

Ala Ala Ala Gly Val Gln Met Lys Leu Glu Phe Leu Gln Arg Lys Phe

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	His His His Ser Ala Ala Gln Pro Leu Val Ser Pro Ile Ser Ala Phe		
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	945	950	955
	Glu Trp Ser Val Trp Gly Ser Trp Tyr Asp Arg Gly Ala Glu Ala Lys		
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	Ser Val Phe His His Ser His Lys His Lys Lys Gln Asp Pro Leu Gln		
	980	985	990
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	995	1000	1005
	Glu Ala Asn Gly Ile Val Glu Cys Gly Pro Cys Gln Lys Val Phe Val		
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	Thr Cys Asp Cys Ser Ile Phe Pro Pro Val Leu Gln Glu Ala Thr Glu		
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	Arg Glu Val Ser Phe Ala Asp Arg Met Lys Trp Ile Ala Cys Asn Asn		
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	Ser Ser Gln Ala Gln Ser Leu Thr Leu Leu Thr Thr Val Ala Met Pro		
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	Val Phe Ser Lys Lys Asn Glu Thr Arg Ser His Gly Ile Leu Leu Gly		
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30	Val Val Gly Ser Asp Val Ala Leu Arg Glu Leu Met Lys Leu Ala Pro		
	515	520	525
	Arg Tyr Lys Leu Gly Val His Gly Tyr Ala Phe Leu Asn Thr Asn Asn		
	530	535	540
35	Gly Tyr Ile Leu Ser His Pro Asp Leu Arg Pro Leu Tyr Arg Glu Gly		
	545	550	555
	Lys Lys Leu Lys Pro Lys Pro Asn Tyr Asn Ser Val Asp Leu Ser Glu		
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	Val Glu Trp Glu Asp Gln Ala Glu Ser Leu Arg Thr Ala Met Ile Asn		
	580	585	590
45	Arg Glu Thr Gly Thr Leu Ser Met Asp Val Lys Val Pro Met Asp Lys		
	595	600	605
	Gly Lys Arg Val Leu Phe Leu Thr Asn Asp Tyr Phe Phe Thr Asp Ile		
	610	615	620
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	625	630	635
	Glu Tyr Ile Leu Leu Gly Asn Thr Ser Val Glu Glu Gly Leu His Asp		
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	Leu Leu His Pro Asp Leu Ala Leu Ala Gly Asp Trp Ile Tyr Cys Ile		
	660	665	670

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 675 680 685
 Ile Arg Phe Leu Thr Arg Lys Asp Pro Asp Leu Glu Cys Asp Glu Glu
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 Thr Pro Glu Asp Glu Ala Ser Val Phe Thr Leu Asp Arg Phe Pro Leu
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 Trp Tyr Arg Gln Ala Ser Glu His Pro Ala Gly Ser Phe Val Phe Asn
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 Lys Ser Val Phe His His Ser His Lys His Lys Lys Gln Asp Pro Leu
 980 985 990

Gln Pro Cys Asp Thr Glu Tyr Pro Val Phe Val Tyr Gln Pro Ala Ile
995 1000 1005

5 Arg Glu Ala Asn Gly Ile Val Glu Cys Gly Pro Cys Gln Lys Val Phe
1010 1015 1020

Val Val Gln Gln Ile Pro Asn Ser Asn Leu Leu Leu Leu Val Thr Asp
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10 Pro Thr Cys Asp Cys Ser Ile Phe Pro Pro Val Leu Gln Glu Ala Thr
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Glu Val Lys Tyr Asn Ala Ser Val Lys Cys Asp Arg Met Arg Ser Gln
15 1060 1065 1070

Lys Leu Arg Arg Arg Pro Asp Ser Cys His Ala Phe His Pro Glu Glu
1075 1080 1085

20 Asn Ala Gln Asp Cys Gly Gly Ala Ser
1090 1095

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